PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#13

In re application of

Hirokazu KUBOTA, et al.

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Appln. No.: 09/773,736

Group Art Unit: 1624

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Filed: February 02, 2001

For: PYRAZOLE DERIVATIVE

SUBMISSION OF PRIORITY DOCUMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Submitted herewith is a certified translation into English of the priority document (Japan P. Hei. 9-279093) on which a claim to priority was made under 35 U.S.C. § 119. The Examiner is respectfully requested to acknowledge receipt of said priority document.

Respectfully submitted,

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Enclosures: Japan P. Hei. 9-279093

Date: July 1, 2003

VERIFICATION OF TRANSLATION

APPLICATION No. Pat. Hei 9-279093

I, Hideki ANAN, of c/o Yamanouchi Pharmaceutical Co., Ltd., Patent Dept., 17-1, Hasune 3-chome, Itabashi-ku, Tokyo 174-8612 Japan, am the translator of the document attached and I state that the following is a true translation to the best of my knowledge and belief.

Signature of translator

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Hideki ANAN

Dated: June 25, 2003

Acknowledgement

October 13, 1997
Commissioner, Patent Office

Identification No.: 100089200

Name(Appellation): Mr. Shozo NAGAI

Filing Date: October 13, 1997

Receipt of the following document is acknowledged.

Item No.	Name of Document	Reference No.	Receipt No.	Notification of Application No. (Indication of Case)
1.	Patent Application	000002772	59700548977	Application No. Hei. 9-279093

End of Document

[Document Name] Application for patent

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[Filing Date] October 13, 1997

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C07D409/04

[Title of the Invention]

Amide or amine derivative

[Number of Claims] 4

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[Deposit Account No.] 005348

[Amount] 21000

[List of Filed Articles]

[Article Name]	Specification	1
[Article Name]	Abstract	1
[No. of General Power of Attorney]	9704254	

[Need of Proof] Yes

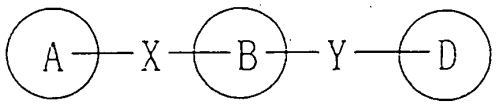
[Name of Document] Specification

[Title of Invention] Amide or amine derivative

[Scope of Claim for Patent]

[Claim 1] An amide or amine derivative represented by the general formula (I):

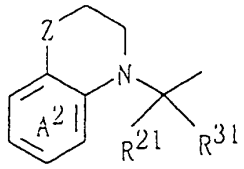
[Chemical formula 1]



(I)

(symbols in the formula having the following meanings:
A represents an aryl group which may be substituted; an aralkyl group which may be substituted; a heteroaryl which may be substituted and which may be condensed, cycloalkyl or lower alkyl group,
X represents a group represented by the formula $-NR^1-CR^2R^3-$ or the formula $-CR^4R^5-NR^6-$ (R^1 and R^6 represent H, OH, lower alkyl, lower alkyl-O- or lower alkyl-CO- group,
R^2 and R^3, R^4 and R^5 may be the same or different, and represent both H or together form an oxo (=O) group),
or A and X together form a group represented by the formula

[Chemical formula 2]



wherein A^2 represents a benzene ring which may be substituted, R^{21} and R^{31} represent similar groups to R^2 and R^3 ; Z represents O or NR^7; R^7 represents H or a lower alkyl group,

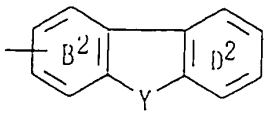
B represents an arylene group which may be substituted or a monocyclic heteroarylene group which may be substituted,

Y represents a single bond, O, S, CO, CS, SO_2 or SO,

D represents an aryl group which may be substituted or a heteroaryl group which may be substituted and which may be condensed,

or B, Y and D together form a group represented by the formula

[Chemical formula 3]

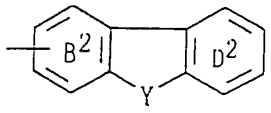


wherein Y has the same definition as described above; B^2 and D^2 represent a benzene ring which may be substituted,

with the proviso that

(i) when Y is a group other than a single bond, B is an arylene group which may be substituted and D is an aryl group which may be substituted, or B, Y and D together form a group represented by the formula

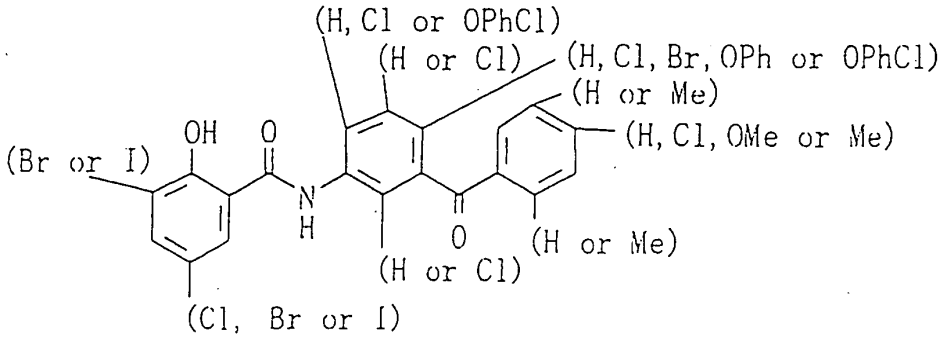
[Chemical formula 4]



wherein Y represents the above-described groups other than a single bond; B^2 and D^2 have the same definitions as described above, and compounds represented by the formulae;

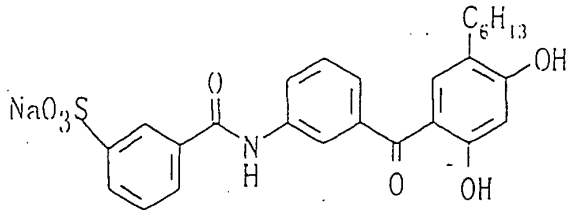
[Chemical formula 5]

(1)



[Chemical formula 6]

(2)



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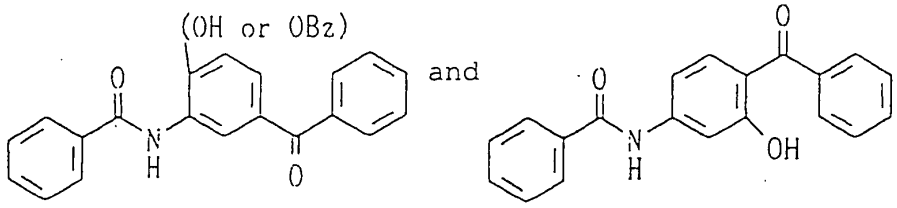

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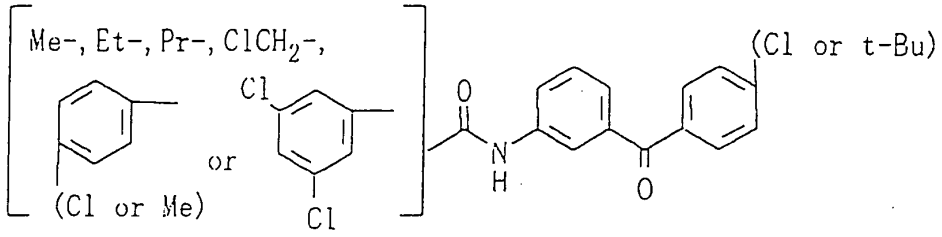

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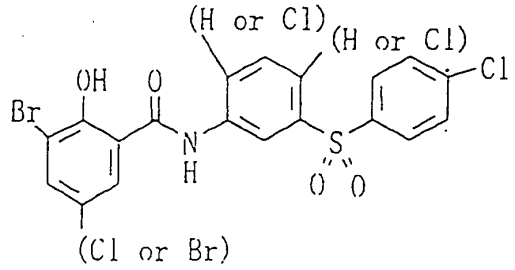
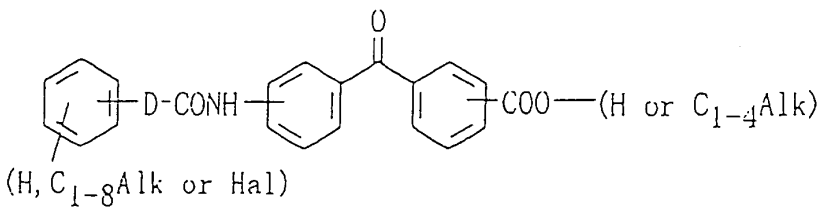
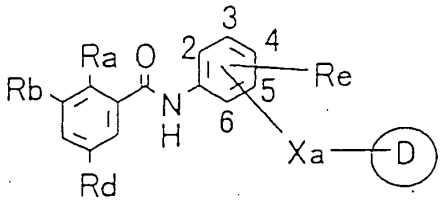


and (6)



wherein Hal represents a halogen atom, OPh represents a phenoxy group, OPhCl represents a p-chlorophenyloxy group, OBz represents a benzoyloxy group, Alk represents an alkyl group, and D represents a single bond or a lower alkylene group; in the formulae, when a position to be substituted can be substituted with one or more kind(s) of substituent(s), substituent(s) are shown in (), as well as the compounds shown in the following table

[Table 1]



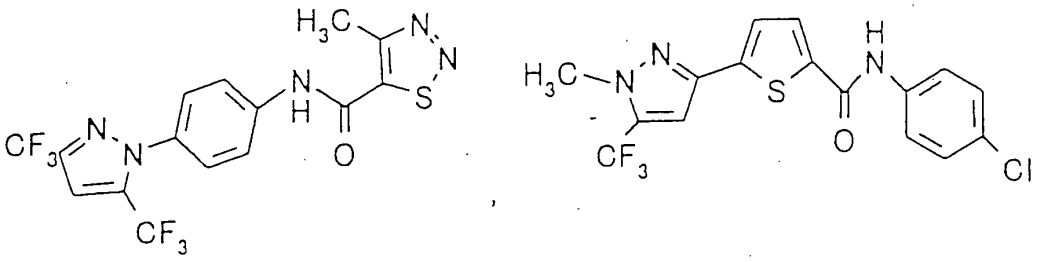
Ra	Rb	Rd	Re	-Xa-D
OH	I	Cl	3-Cl	4-O-(1-Cl-2-Naph)
OH	I	Cl	3-Cl	4-O-(2-Cl-1-Naph)
OH	I	Cl	5-Cl	2-O-(1-Br-2-Naph)
OH	Br	Br	5-Cl	2-O-(2-Cl-1-Naph)
OH	H	Cl	3-Cl	4-CO-(4-Cl-Ph)
OH	H	Cl	3-Cl	4-O-(1-Cl-2-Naph)
OH	H	Cl	3-Cl	4-O-(4-Cl-1-Naph)
OH	H	Cl	5-Cl	2-O-Ph
OH	I	I	4-Cl	3-O-(4-Cl-1-Naph)
OH	I	I	H	2-O-(2-iPr-5-Me-Ph)
OH	Br	Cl	4-Cl	3-CO-Ph
OH	I	I	4-Cl	3-CO-(4-Me-Ph)
OH	I	I	4-Cl	3-CO-(4-Cl-Ph)
OH	Br	Br	4-O-(4-Cl-Ph)	3-CO-(4-Cl-Ph)

wherein Ph represents a phenyl group, Naph represents a naphthyl group, and iPr represents an isopropyl group, are excluded, or

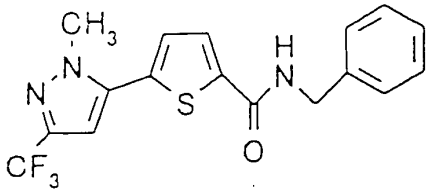
(ii) when Y is a single bond, B is an unsubstituted arylene group or a monocyclic heteroarylene group which may be substituted, D is a heteroarylene group which may be

substituted and which may be condensed, and compounds having the formulae

[Chemical formula 7]



and

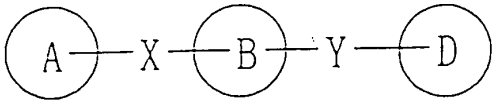


are excluded), or a pharmaceutically acceptable salt thereof.

[Claim 2] A medicament comprising, as an active ingredient, an amide or amine derivative described in claim 1 or a pharmaceutically acceptable salt thereof.

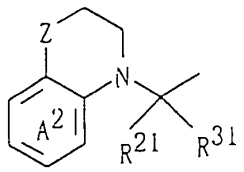
[Claim 3] A Ca^{2+} release-activated Ca^{2+} channel inhibitor comprising, as an active ingredient, an amide or amine derivative represented by the general formula (I') or a pharmaceutically acceptable salt thereof.

[Chemical formula 8]



(I')

(symbols in the formula having the following meanings:
A represents an aryl group which may be substituted; an aralkyl group which may be substituted; a heteroaryl which may be substituted and which may be condensed, cycloalkyl or lower alkyl group,
X represents a group represented by the formula $-NR^1-CR^2R^3-$ or the formula $-CR^4R^5-NR^6-$ (R^1 and R^6 represent H, OH, lower alkyl, lower alkyl-O- or lower alkyl-CO- group,
R^2 and R^3, R^4 and R^5 may be the same or different, and represent both H or together form an oxo (=O) group),
or A and X together form a group represented by the formula
[Chemical formula 9]



wherein A^2 represents a benzene ring which may be substituted, R^{21} and R^{31} represent similar groups to R^2 and

R^3; Z represents O or NR^7; R^7 represents H or a lower alkyl group,

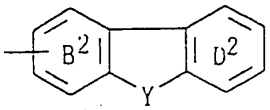
B represents an arylene group which may be substituted or a monocyclic heteroarylene group which may be substituted,

Y represents a single bond, O, S, CO, CS, SO_2 or SO,

D represents an aryl group which may be substituted or a heteroaryl group which may be substituted and which may be condensed,

or B, Y and D together form a group represented by the formula

[Chemical formula 10]



wherein Y has the same definition as described above; B^2 and D^2 represent a benzene ring which may be substituted).

[Claim 4] An agent as claimed in Claim 3, wherein it is a selective Ca^{2+} release-activated Ca^{2+} channel inhibitor.

[Detailed Description of the Invention]

[0001]

[Industrially Applicable Field]

The present invention relates to a medicament, particularly a Ca^{2+} release-activated Ca^{2+} channel inhibitor useful for prevention or treatment of inflammatory

diseases, allergic diseases, and the like with which Ca^{2+} release-activated Ca^{2+} channel is concerned.

[0002]

[Background Art]

It has been known for a long time that calcium ion (Ca^{2+}) is important for an intracellular messenger mechanism in the activation of various cells. Intracellular Ca^{2+} also acts as an important regulatory factor in inflammatory cells. It has been suggested, however, that voltage-operated Ca^{2+} channel (referred to as "VOCC" hereinafter) inhibitors such as nifedipine which has been known as an agent of Ca^{2+} antagonist do not show inhibitory activity against the activation of inflammatory cells and that a Ca^{2+} influx mechanism other than VOCC exists in inflammatory cells.

[0003]

Hoth et al. have reported that a Ca^{2+} -selective and Ca^{2+} store depletion-activated Ca^{2+} channel, namely Ca^{2+} release-activated Ca^{2+} channel (to be abbreviated as "CRACC" hereinafter; also called Ca^{2+} store-dependent Ca^{2+} channel) is present in mast cells and lymphocytes, and these cells are insensitive to membrane potential (Pflugers Arch., 430, pp. 315 - 322 (1995)). It is known that CRACC is present in almost all inflammatory cells such as mast cells, lymphocytes, astrocytes (J. Biol. Chem., 270, pp. 29 - 32 (1995)) and the like, and that it is deeply concerned

in, for example, cytokine production and lipid mediator release (J. Immunol., 155, pp. 285 -296 (1995) and Br. J. Pharmacol., 144, pp. 598 - 601 (1995)).

[0004]

Recently, it has been revealed that an anti-rheumatoid arthritis agent tenidap has a potency of CRACC inhibitor (Cell Calcium, 14, pp. 1 - 16 (1993)). Therefore, a CRACC inhibitor has a possibility of therapeutic potency on chronic inflammatory diseases including rheumatoid arthritis.

It is known that CRACC is also present in endothelial cells (Am. J. Physiol., 269, C 733 - 738 (1995)) and epithelial cells (J. Biol. Chem., 270, pp. 169 - 175 (1995)). Since it has been reported that sustained calcium influx takes a role in the radical affection of endothelial cells (Am. J. Physiol., 261, C 889 - 896 (1991)), it is suggested that a CRACC inhibitor should have protective efficacy on endothelial cell-concerned tissue damage.

[0005]

In addition, it has been reported that blockage of calcium influx inhibited cell proliferation and interleukin 2 (IL-2) production (Br. J. Pharmacol., 133, pp. 861 - 868 (1994)). Therefore, a CRACC inhibitor is useful as an agent for the prevention and treatment of proliferative or progressive diseases (e.g., malignant tumor and the like)

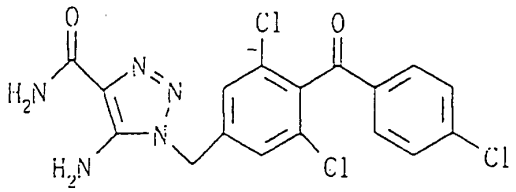
and autoimmue diseases, and also as a suppresser for tissue rejection in transplantation.

On the other hand, it is known that in excitable cells such as smooth muscle cells and nerve cells, intracellular calcium is regulated with VOCC, but CRACC is not concerned therewith. Therefore, it is expected that a calcium channel blacker having CRACC selectivity against VOCC should be an useful agent for the prevention or treatment of various inflammatory diseases, allergic diseases, tissue damages, proliferative diseases and the like without undesirable actions on cardiovascular and central nervous system.

[0006]

Recently, some compounds showing CRACC inhibitory activity have been reported, such as a cycloalkyl-piperazinylethanol derivative disclosed in a published German patent publication 4404249 and a 2-(3,4-dihydro-1-isoquinolyl)acetamide derivative disclosed in WO 94/00435. While, in J. Pharm. Exp. Ther., 257, p967-971 (1991), a compound represented by the following formula and having CRACC inhibitory activity (hereinafter, referred to as compound W) is disclosed.

[Chemical formula 11]



[0007]

[Problems to be Solved by the Invention]

However, in the conventional reports, any reference has not been made regarding the selectivity of the compound having CRACC inhibitory activity and there are no reports on a compound whose CRACC selectivity over VOCC has been confirmed.

Therefore, it is earnestly expected to develop a potent CRACC inhibitor effective for the prevention or treatment of various inflammatory diseases, allergic diseases, tissue damages, proliferative diseases and the like, particularly those further having a high CRACC selectivity over VOCC.

[0008]

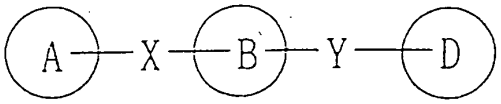
[Means for Solving the Problems]

The inventors of the present invention have conducted extensive studies on the screening of compounds having excellent CRACC inhibitory activity. As a result of the efforts, certain amide or amine derivatives which possess entirely different structures from those of the reported CRACC inhibitors have been found to show excellent CRACC inhibitory activity. The present invention has been accomplished by further finding that these compounds have high CRACC selectivity over VOCC.

[0009]

Accordingly, this invention relates to a novel amide or amine derivative represented by the following general formula (I) or a pharmaceutically acceptable salt thereof, as well as a medicament including thereof as an active ingredient.

[Chemical formula 12]



(I)

(symbols in the formula having the following meanings:

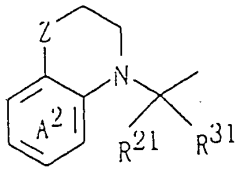
A represents an aryl group which may be substituted; an aralkyl group which may be substituted; a heteroaryl which may be substituted and which may be condensed, cycloalkyl or lower alkyl group,

X represents a group represented by the formula $-NR^1-CR^2R^3-$ or the formula $-CR^4R^5-NR^6-$ (R^1 and R^6 represent H, OH, lower alkyl, lower alkyl-O- or lower alkyl-CO- group,

R^2 and R^3, R^4 and R^5 may be the same or different, and represent both H or together form an oxo (=O) group),

or A and X together form a group represented by the formula

[Chemical formula 13]



wherein A^2 represents a benzene ring which may be substituted, R^{21} and R^{31} represent similar groups to R^2 and R^3 ; Z represents O or NR^7; R^7 represents H or a lower alkyl group,

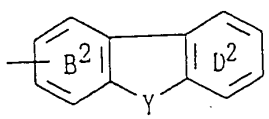
B represents an arylene group which may be substituted or a monocyclic heteroarylene group which may be substituted,

Y represents a single bond, O, S, CO, CS, SO_2 or SO,

D represents an aryl group which may be substituted or a heteroaryl group which may be substituted and which may be condensed,

or B, Y and D together form a group represented by the formula

[Chemical formula 14]

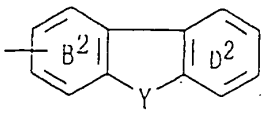


wherein Y has the same definition as described above; B^2 and D^2 represent a benzene ring which may be substituted,

with the proviso that

(i) when Y is a group other than a single bond, B is an arylene group which may be substituted and D is an aryl group which may be substituted, or B, Y and D together form a group represented by the formula

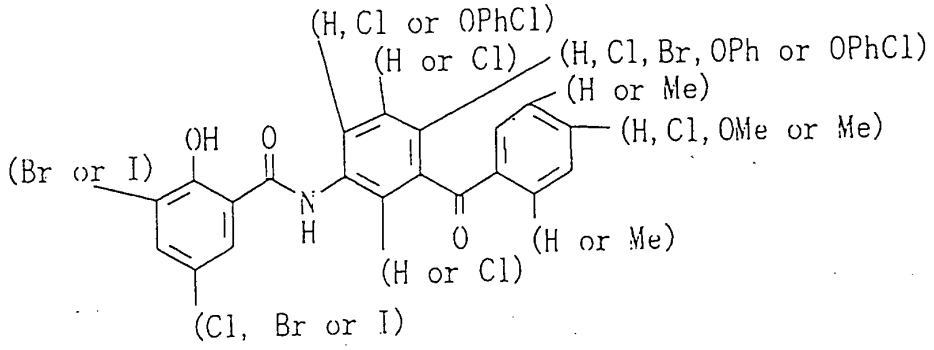
[Chemical formula 15]



wherein Y represents the above-described groups other than a single bond; B^2 and D^2 have the same definitions as described above, and compounds represented by the formulae;

[Chemical formula 16]

(1)



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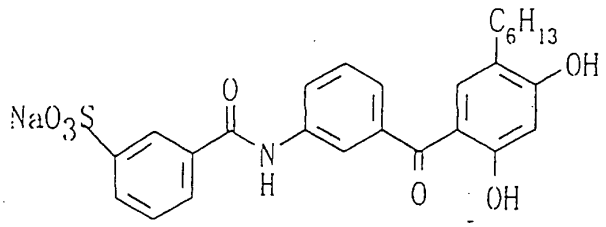

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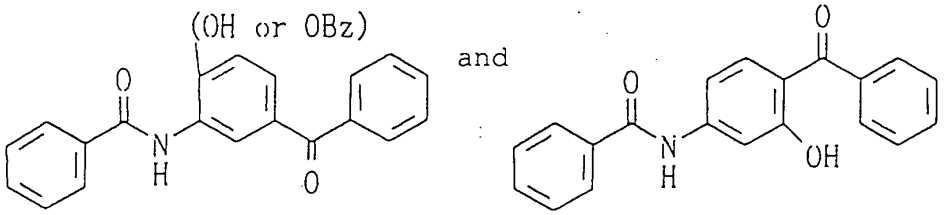

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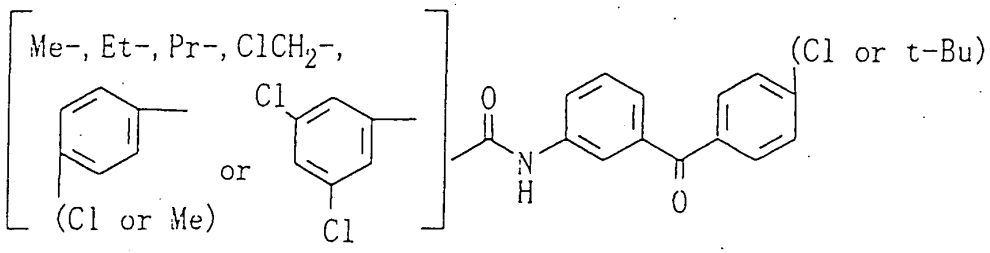
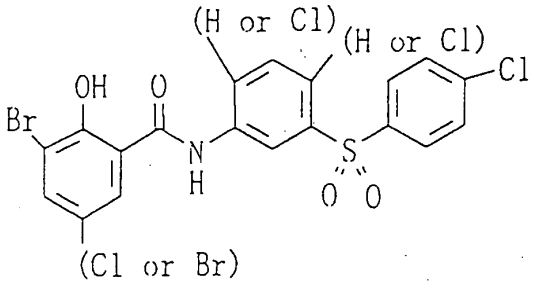
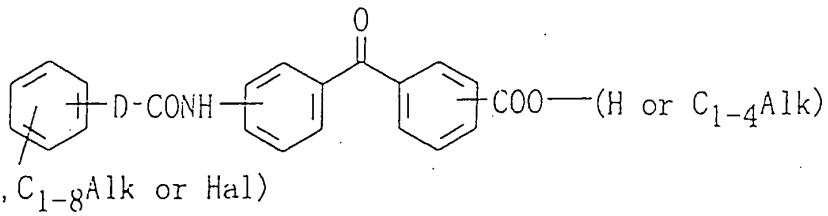


[Chemical formula 17]

(5)

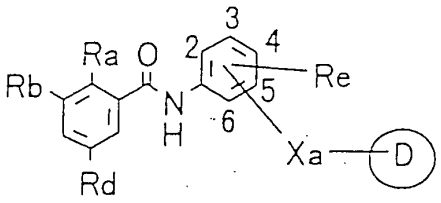


and (6)



wherein Hal represents a halogen atom, OPh represents a phenoxy group, OPhCl represents a p-chlorophenyloxy group, OBz represents a benzoyloxy group, Alk represents an alkyl group, and D represents a single bond or a lower alkylene group; in the formulae, when a position to be substituted can be substituted with one or more kind(s) of substituent(s), substituent(s) are shown in (), as well as the compounds shown in the following table

[Table 2]

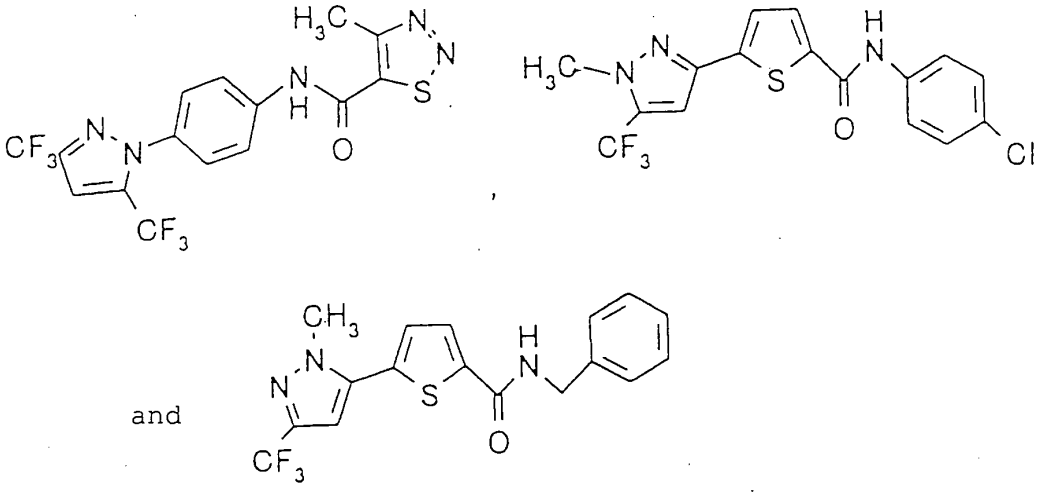


Ra	Rb	Rd	Re	-Xa-D
OH	I	Cl	3-Cl	4-O-(1-Cl-2-Naph)
OH	I	Cl	3-Cl	4-O-(2-Cl-1-Naph)
OH	I	Cl	5-Cl	2-O-(1-Br-2-Naph)
OH	Br	Br	5-Cl	2-O-(2-Cl-1-Naph)
OH	H	Cl	3-Cl	4-CO-(4-Cl-Ph)
OH	H	Cl	3-Cl	4-O-(1-Cl-2-Naph)
OH	H	Cl	3-Cl	4-O-(4-Cl-1-Naph)
OH	H	Cl	5-Cl	2-O-Ph
OH	I	I	4-Cl	3-O-(4-Cl-1-Naph)
OH	I	I	H	2-O-(2-iPr-5-Me-Ph)
OH	Br	Cl	4-Cl	3-CO-Ph
OH	I	I	4-Cl	3-CO-(4-Me-Ph)
OH	I	I	4-Cl	3-CO-(4-Cl-Ph)
OH	Br	Br	4-O-(4-Cl-Ph)	3-CO-(4-Cl-Ph)

wherein Ph represents a phenyl group, Naph represents a naphthyl group, and iPr represents an isopropyl group, are excluded (in the Table, 1-chloro-2-naphthyl group is abbreviated as 1-Cl-2-Naph, and the other groups are also abbreviated similarly; the same applies hereinafter), or (ii) when Y is a single bond, B is an unsubstituted arylene group or a monocyclic heteroarylene group which may be

substituted, D is a heteroarylene group which may be substituted and which may be condensed, and compounds having the formulae

[Chemical formula 18]



and

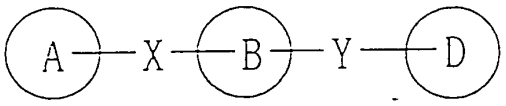
are excluded; the same applies hereinafter).

[0010]

Further, this invention relates to a Ca^{2+} release activated Ca^{2+} channel (CRACC) inhibitor comprising, as an active ingredient, an amide or amine derivative represented by the following general formula (I') or a pharmaceutically acceptable salt thereof. Particularly, it relates to a selective CRACC inhibitor having CRACC selectivity over voltage-operated Ca^{2+} channel (VOCC).

[0011]

[Chemical formula 19]



(I')

(symbols in the formula having the following meanings:

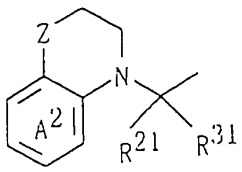
A represents an aryl group which may be substituted; an aralkyl which may be substituted; a heteroaryl which may be substituted and which may be condensed, cycloalkyl or lower alkyl,

X represents a group represented by the formula $-NR^1-CR^2R^3-$ or the formula $-CR^4R^5-NR^6-$ (R^1 and R^6 represent H, OH, lower alkyl, lower alkyl-O- or lower alkyl-CO- group,

R^2 and R^3, R^4 and R^5 may be the same or different, and represent both H or together form an oxo (=O) group),

or A and X together form a group represented by the formula

[Chemical formula 20]



wherein A^2 represents a benzene ring which may be substituted, R^{21} and R^{31} represent similar groups to R^2 and

R^3 ; Z represents O or NR^7; R^7 represents H or a lower alkyl group,

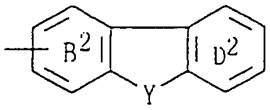
B represents an arylene group which may be substituted or a monocyclic heteroarylene group which may be substituted,

Y represents a single bond, O, S, CO, CS, SO_2 or SO,

D represents an aryl group which may be substituted or a heteroaryl group which may be substituted and which may be condensed,

or B, Y and D together form a group represented by the formula

[Chemical formula 21]



wherein Y has the same definition as described above; B^2 and D^2 represent a benzene ring which may be substituted; the same applies hereinafter).

[0012]

[Embodiments of the Invention]

The present invention will be described in detail below.

Unless otherwise noted, the term "lower" as used in the definition of groups in general formulae in this specification means a straight or branched carbon chain having 1 to 6 carbon atoms. Accordingly, as the "lower

alkyl group", mention may be made of alkyl groups having 1 to 6 carbon atoms, specifically methyl and ethyl group; straight chain or branched propyl, butyl, heptyl and hexyl group.

In the present specification, the "aryl group" means six- to fourteen-membered aromatic hydrocarbon groups. Specifically, for example, phenyl, naphthyl, indenyl, and anthryl group can be mentioned. A phenyl group and a naphthyl group are preferable.

[0013]

The "aralkyl group" is the group wherein an optional hydrogen atom of the above-described lower alkyl group is substituted with the above-described aryl group, preferably a benzyl group.

The "heteroaryl group which may be condensed" means a monocyclic heteroaryl group or condensed five- or six-membered heteroaryl group which comprise one or more hetero atoms selected from an oxygen atom, a sulfur atom and a nitrogen atom. The condensed five- or six-membered heteroaryl group herein means a group obtained by condensing one benzene ring with a five- or six-membered heteroaryl ring or a bicyclic group obtained by condensing two five- or six-membered heteroaryl rings with each other.

The five- or six-membered monocyclic heteroaryl group is a five- or six-membered monocyclic heteroaryl group comprising 1 to 4 hetero atom(s) selected from a nitrogen

atom, a sulfur atom and an oxygen atom. Specifically, mention may be made of furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isooxazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridyl, pyrimidinyl, pyridazinyl, and pyrazinyl. These groups can be partially hydrogenated. As the partially hydrogenated groups, for example, mention may be made of pyrrolinyl, imidazolinyl, pyrazolinyl, dihydropyridyl, tetrahydropyridyl, dihydropyrimidinyl and dihydropyridazinyl.

[0014]

As the condensed five- or six-membered heteroaryl group, mention may be made of, for example, indolyl, indazolyl, benzofuranyl, isobenzofuranyl, benzothienyl, isoindolyl, isoquinolyl, chromenyl, quinolyl, quinazolinyl, benzimidazolyl, benzthiazolyl, benzoxazolyl, benztriazolyl, benzoxadiazolyl, phthalazinyl, quinoxanyl and cinnolinyl, which form a condensed ring with a benzene ring; and groups obtained by condensing two optional heteroaryl groups as described above such as imidazo[1,2-a]pyridinyl, pyradino[2,3-d]pyridazinyl, 4H-imidazo[4,5-d]thiazolyl and pyroo[2,3-b]pyridyl groups. These groups can be partially hydrogenated and as the partially hydrogenated groups, for example, an indolinyl group, tetrahydroquinolyl and dihydroquinoxalinyl group can be mentioned.

The "arylene group" is a divalent group formed by further excluding one optional hydrogen group from the above-described aryl group. As the arylene group, preferably mention made of 1,4-phenylene, 1,3-phenylene, and 1,2-phenylene.

The "monocyclic heteroarylene group" is a divalent group formed by further excluding one optional hydrogen group from the above-described monocyclic five- or six-membered heteroaryl group. Preferable examples thereof include furandiyl, thiophenediyl, pyrrolediyl, imidazolediyl, thiazolediyl, oxazolediyl and pyridinediyl. A five-membered heteroaryl group is preferable. Thiophenediyl is particularly preferable.

[0015]

The "cycloalkyl group" is a cycloalkyl group having 3 to 8 carbon atoms. Specifically, mention may be made of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl group.

As the substituents in the "aryl group which may be substituted", the "aralkyl group which may be substituted", and the "heteroaryl group which may be substituted and which may be condensed", any substituent can be used as long as they can be currently used in these groups. As these substituents, for example, mention may be made of hydroxyl group; halogen atom (for example, Cl, Br, F, I); lower alkyl which may be substituted with one or more

halogen atoms, lower alkenyl, lower alkynyl, cycloalkyl, lower alkyl-O-, lower alkyl-O-CO-, carbonyl, nitro, cyano, amino, mono-lower alkyl-amino, di-lower alkyl-amino, lower alkyl-CO-, lower alkyl-CONH-, lower alkyl-CO-O-, mercapto, lower alkyl-thio, lower alkyl-sulfinyl, lower alkyl-sulfonyl, aminosulfonyl, carbamoyl, mono-lower alkyl-amino-CO-, di-lower alkyl-amino-CO-, methylenedioxy, ethylenedioxy, propylenedioxy and aralkyl group.

When Y is a single bond, B and D directly bond each other.

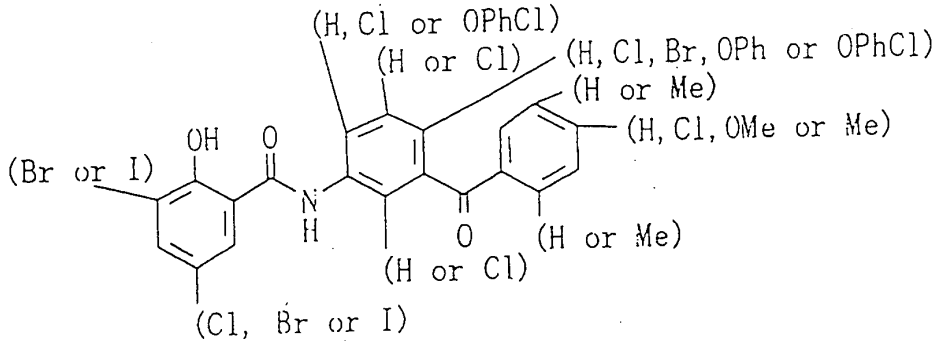
[0016]

Examples of an amide and amine derivative which are to be active components of CRACC inhibitor of the present invention include the following known compounds.

It should be noted that in the following formulae and tables, Hal represents a halogen atom, Ph represents a phenyl group, OPh represents a phenoxy group, OPhCl represents a p-chlorophenyloxy group, OBz represents a benzoyloxy group, Alk represents an alkyl group, D represents a single bond or a lower alkylene group, Naph represents a naphthyl group, iPr represents an isopropyl group, Comp represents a sales company, and CN represents a code number. In the formulae, when a position to be substituted can be substituted with one or more kind(s) of substituent(s), substituent(s) are shown in ().

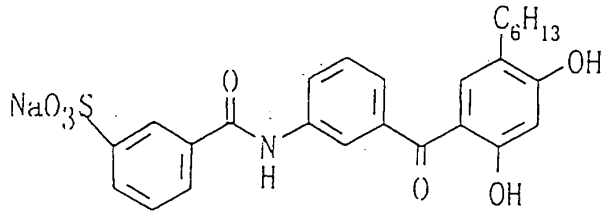
(1) In Soviet patent SU807609; SU1327487 and SU1026420 as well as in Med Parazitol Parazit Bolezni 1995 (6) 41-42, ibid 1991 (4) 43-46 and Biofizika 1981 26 (6) 995-998, the compound having the following formula and having an anti-parasite activity is described.

[Chemical formula 22]



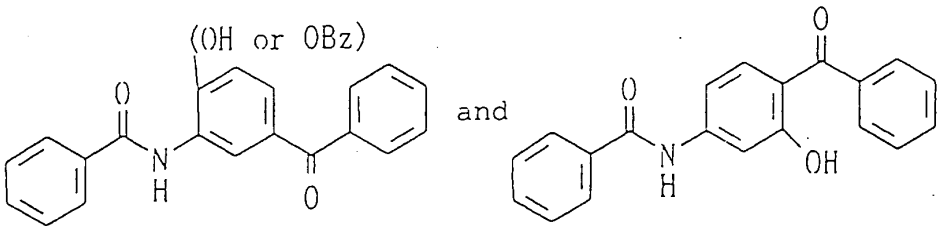
(2) In JP-A-63-56652 (The term "JP-A" as used herein means an "unexamined published Japanese patent application"), the following compound is described as a photographic material.

[Chemical formula 23]



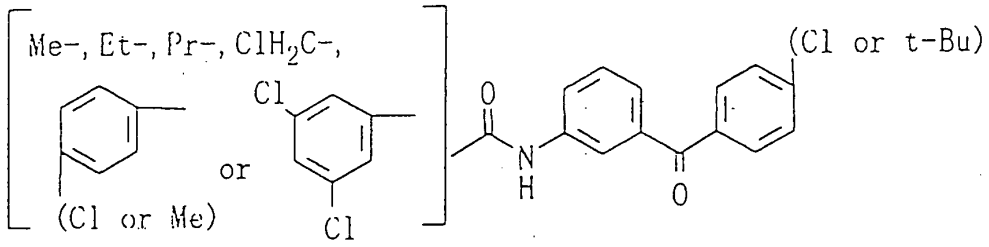
(3) In MAN-MADE TEXTILES IN INDIA 1998, 287, the compound having the following formula and ultraviolet absorption function is described.

[Chemical formula 24]



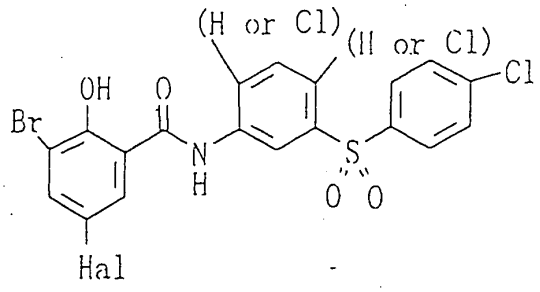
(4) In Farmaco. Ed. Sci., 1998 43 (6) 517-522, the compound having the following formula and anti-eumycetes activity is described.

[Chemical formula 25]



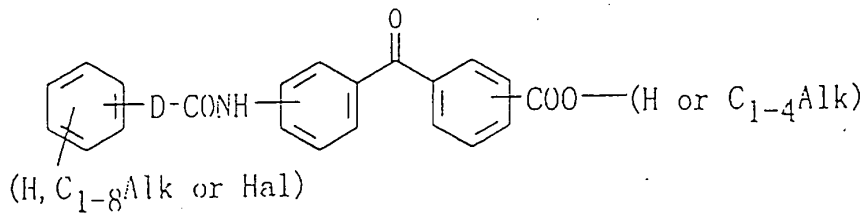
(5) In ibid 1991 (4) 43-46, the compound having the following formula and an anti-parasite activity is described.

[Chemical formula 26]



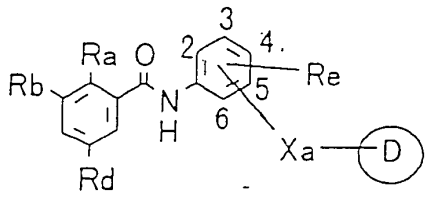
(6) In JP-A-3-258749, the compound having the following formula and an PLA_2 inhibitory activity is described.

[Chemical formula 27]



(7) The compounds shown in the following table are commercially available.

[Table 3]



Compound	Comp	CN	Ra	Rb	Rd	Re	-Xa-D
A	CSC	075-0075	OH	I	Cl	3-Cl	4-O-(1-Cl-2-Naph)
B	AsIn	JSU0006018	OH	I	Cl	3-Cl	4-O-(2-Cl-1-Naph)
C	CSC	075-086	OH	I	Cl	5-Cl	2-O-(1-Br-2-Naph)
D	SPE	AG-690/ 3065046	OH	Br	Br	5-Cl	2-O-(2-Cl-1-Naph)
E	LT	16694	OH	H	Cl	3-Cl	4-CO-(4-Cl-Ph)
F	LT	16646	OH	H	Cl	3-Cl	4-O-(1-Cl-2-Naph)
G	CSC	121-124	OH	H	Cl	3-Cl	4-O-(4-Cl-1-Naph)
H	CSC	141-257	OH	H	Cl	5-Cl	2-O-Ph
I	CSC	075-074	OH	I	I	4-Cl	3-O-(4-Cl-1-Naph)
J	CSC	075-111	OH	I	I	H	2-O-(2-iPr-5-Me-Ph)
K	CSC	180-436	OH	Br	Cl	4-Cl	3-CO-Ph
L	LT	16668	OH	I	I	4-Cl	3-CO-(4-Me-Ph)
M	CSC	121-047	OH	I	I	4-Cl	3-CO-(4-Cl-Ph)
N	LT	16668	OH	Br	Br	4-O-(4-Cl-Ph)	3-CO-(4-Cl-Ph)

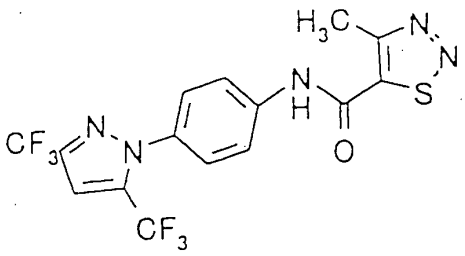
(In the table, names of the sales companies (domicile) are as follows:

LT: Labo Test (Freiberg, Germany), CSC: CONTACT-SERVICE COMPANY (Moscow Region, Russia), AsIn: AsInEx (Moscow, Russia), and SPE: SPECS (The Netherlands, Rijswijk)

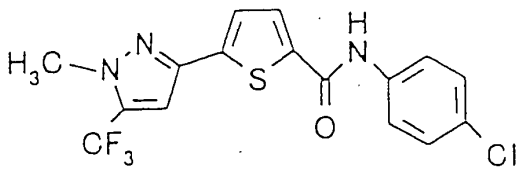
(8) The following compounds are commercially available from MAYBRIDGE (UK. Cornwall) K.K. In (), code numbers are shown.

[Chemical formula 28]

Compound P (SEW04225)

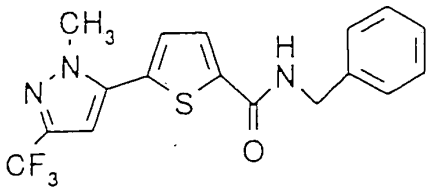


Compound Q (KM02904)



Compound R (KM03000)

and



[0017]

The compound of this invention may exist in the form of geometrical isomers or tautomers depending on the kind of substituent groups, and these isomers in separate forms or mixtures thereof are included in the present invention.

Also, the compound of the present invention may have asymmetric carbon atoms, so that it may exist in (R) and

(S) optical isomer forms based on such carbon atoms. All of the mixtures and the isolated forms of these optical isomers are included in the present invention.

The compound (I) of this invention may form an acid addition salt or, depending on the kind of substituents, a salt with a base. Such salts are pharmaceutically acceptable ones, and their examples include acid addition salts with inorganic acids (e.g., hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, phosphoric acid and the like) or with organic acids (e.g., formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, malic acid, tartaric acid, citric acid, methanesulfonic acid, ethanesulfonic acid, aspartic acid, glutamic acid and the like) and salts with inorganic bases (e.g., sodium, postassium, magnesium, calcium, aluminum and the like) or with organic bases (e.g., methylamine, ethylamine, ethanolamine, lysine, ornithine and the like), as well as ammonium salts.

In addition, various hydrates and solvates and polymorphism of the compound (I) and the salts thereof are also included in this invention.

[0018]

[Production Method]

The compound of the present invention and a pharmaceutically acceptable salt thereof can be produced by

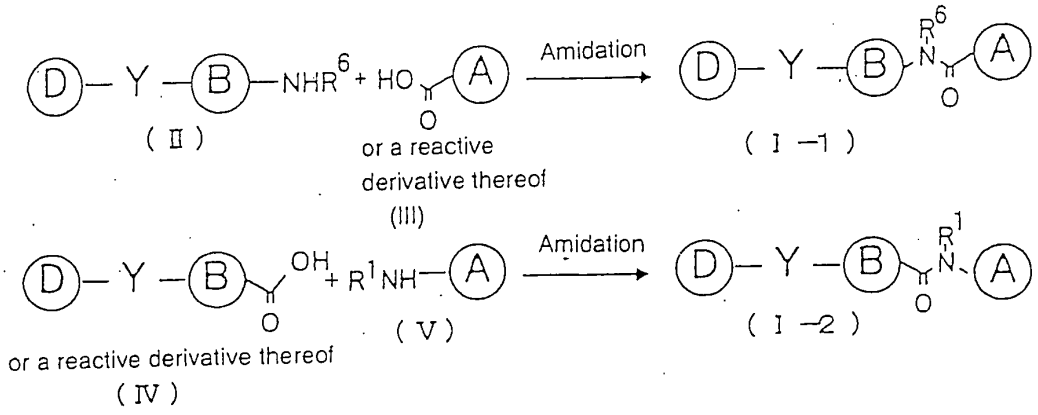
making use of the features of its basic structure or the kind of its substituents and by employing various known synthesis methods. In that case, depending on the kind of each functional group, it may sometimes be effective from the viewpoint of production techniques to replace said functional group with an appropriate protecting group, namely a group which can be converted into said functional group easily, at the stage of raw materials or intermediates. Thereafter, the compound of interest can be obtained by removing the protecting group as occasion demands. Examples of such functional groups include a hydroxyl group, a carboxyl group and the like and examples of their protecting group include those which are described in "Protective Group in Organic Synthesis", 2nd edition, edited by Greene and Wuts, which may be optionally used depending on the reaction conditions.

[0019]

The following describes typical methods for the preparation of the compound of the present invention.

Production Method 1

[Chemical formula 29]



(II)　　(III)　　(I -1)

(IV)　　(V)　　(I -2)

In this method, as shown in the above reaction formula, the compound (I-1) or (I-2) of the present invention is obtained by subjecting an amine derivative represented by the general formula (II) or (V) and a carboxylic acid derivative represented by the general formula (III) or (IV) to amidation reaction.

The carboxylic acid derivative (III) or (IV) which can be used in the production method 1 is a free carboxylic acid or a reactive derivative thereof, and examples of the reactive derivative include acid halides such as acid chloride, acid bromide and the like; acid azides; active esters which can be prepared using methanol, ethanol, benzyl alcohol, phenol which may be substituted, 1-hydroxybenzotriazole, N-hydroxysuccinimide and the like; symmetric acid anhydrides; and mixed acid anhydrides with alkylcarboxylate, p-toluenesulfonic acid and the like.

These reactive derivatives are commercially available or can be produced by the usual procedures.

The amidation reaction can be carried out by the usual procedures.

[0020]

When the reaction is carried out using a free carboxylic acid, are preferably used a condensing agent such as N,N'-dicyclohexylcarbodiimide (DCC), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (WSCD) or the like; or a carboxylic acid activating agent such as 1,1'-carbonyldiimidazole, N,N'-disuccinimidyl carbonate, N,N'-bis(2-oxo-3-oxazolidinyl)phosphinic chloride, diphenylphosphoryl azide, diethylphosphorocyanidate, phosphorus oxychloride, phosphorus trichloride, triphenylphosphine/N-bromosuccinimide (NBS) or the like.

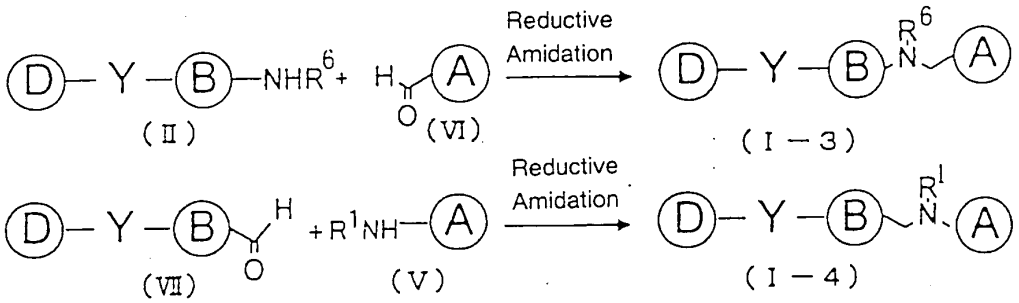
The reaction is carried out using an amine derivative represented by the general formula (II) or (V) and a carboxylic acid derivative represented by the general formula (III) or (IV), in equimolar amounts or one of them in excess amount, in a reaction inert organic solvent such as pyridine, tetrahydrofuran (THF), dioxane, ether, benzene, toluene, xylene, dichloromethane, dichloroethane, chloroform, N,N-dimethylformamide (DMF), ethyl acetate, acetonitrile or the like. The reaction temperature is optionally selected depending upon a kind of reaction derivatives.

Depending on a kind of reaction derivatives, addition of a base such as triethylamine, pyridine, picoline, N,N-dimethylaniline, potassium carbonate, sodium hydroxide or the like may be advantageous in some cases from the viewpoint of accelerating the reaction. It is possible to use pyridine also as the solvent.

[0021]

Production Method 2

[Chemical formula 30]



In this method, as shown in the above reaction formula, the compound (I-3) or (I-4) of the present invention is obtained by subjecting an amine derivative represented by the general formula (II) or (V) and an aldehyde derivative represented by the general formula (VI) or (VII) to reductive amination reaction.

This reductive amination reaction is carried out by reacting both compounds in an inert solvent as in the amidation in the production method 1, then isolating or unisolating the resulting Schiff's base, followed by

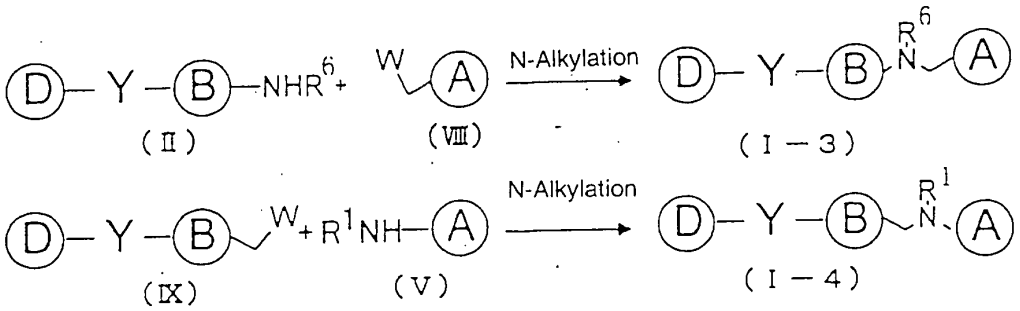
reducing the Schiff's base. The formation of Schiff's base is advantageously effected by removing water to be formed in the presence of a Lewis acid such as titanium (IV) isopropoxide, titanium (IV) chloride, and boron trifluoride-diethylether complex; a catalyst such as p-toluenesulfonic acid, adipic acid, acetic acid or hydrochlric acid; or a dehydrating agent such as molecular sieves or potassium hydroxide, or using a Dean-Stark trap. The reaction temperature is optionally determined. However, room temperature to under reflux is preferable.

The reduction of Schiff's base can be effected by adding a metallic hydrogenated complex (sodium cyanoborohydride, sodium triacetoxyborohydride, sodium borohydride, and the like) or a reducing agent such as borane at a temperature of from -20°C to reflux temperature. Alternatively, it can be effected by a reaction at 0°C to 100°C in the presence or absence of an acid such as acetic acid or hydrochloric acid, using a reduction catalyst (e.g., palladium on carbon, Raney nickel, and the like) in a solvent such as methanol, ethanol, ethyl acetate or acetic acid, in a hydrogen atmosphere of atmospheric pressure to 50 kg/cm^2.

[0022]

Production Method 3

[Chemical formula 31]



(In the above reaction formula, W represents a currently used elimination group such as a halogen atom or an organic sulfonic residue.)

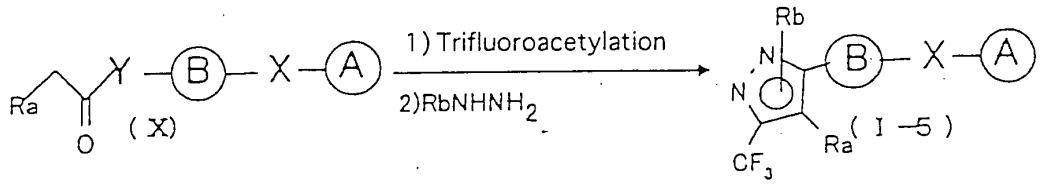
In this method, the compound (I-3) or (I-4) of the present invention is obtained by subjecting an amine derivative represented by the general formula (II) or (V) to an alkylation with a compound represented by the general formula (VIII) or (IX).

This N-alkylation can be effected in the presence or absence of a base such as potassium carbonate, triethyl amine or sodium hydride in an inert solvent such as DMF, acetone, 2-butanone or acetonitrile or in the absence of a solvent, under cooling to reflux.

[0023]

Production Method 4

[Chemical formula 32]



(In the above formula, each Ra and Rb represents H or a lower alkyl group.)

In this production method, the compound (I-5) of the present invention is obtained by carrying out trifluoroactylation of the carbon atom adjacent to the ketone of a compound represented by the general formula (X) and then effecting cyclization by reacting it with a hydrazine derivative.

The first step trifluoroacetylation can be carried out by allowing the compound to react with a trifluoroacetylation agent (for example, ethyl trifluoroacetate, trifluoroacetic anhydride or the like) at a temperature of from -78°C to reflux temperature in a solvent such as methanol, ethanol, 1,3-dimethylimidazolidin-2-one, THF, DMF or the like, in the presence of a base such as sodium methoxide, sodium ethoxide, alkali metal hexamethyldisilazide, sodium

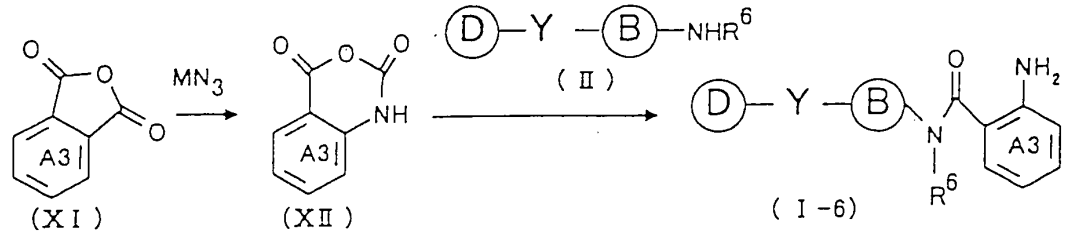
hydride, alkyl lithium, phenyl lithium, lithium diisopropylamide, triethylamine or the like.

The second step cyclization reaction can be carried out by allowing the compound obtained in the first step to react with a hydrazine derivative in a solvent such as methanol, ethanol or the like, or without solvent, in the presence or absence of an acid such as acetic acid, hydrochloric acid or the like or a Lewis acid such as titanium (IV) isopropoxide, titanium (IV) chloride, boron trifluoride-diethyl ether complex or the like. This reaction can be carried out at a temperature of cooling temperature to under reflux while heating.

[0024]

Production Method 5

[Chemical formula 33]



(in the above reaction, M represents Na or a trimethylsilyl group, A3 represents a benzene ring which may be substituted.)

In this production method, the compound (I-6) of the present invention is obtained by carrying out transfer reaction of an anhydrous phthalic derivative represented by the general formula (XI) to give a compound represented by the general formula (XII) via an acid azide, which is then subjecting to amidation using a compound represented by the general formula (II).

The transfer reaction via an acid azide of the first step can be carried out using sodium azide, trimethylsilyl azide or the like, in the presence or absence of a base such as triethylamine, in a solvent such as acetonitrile, dichloromethane, 1,2-dichloroethane, DMF, toluene, benzene or the like at a temperature of from -78°C to reflux temperature. The amidation in the second step can be effected as in the production method 1.

[0025]

Other production methods

N-alkylation of a nitrogen atom of an amino group or an amide group of X can be effected as in the above-described production method 3. N-alkylation of a ring-nitrogen atom of A, B or D can be effected as well. The introduction of a substituent to each ring, modification of a group, and elimination of a protective group can be carried out according to a conventional method.

[0026]

Starting compounds of the present invention are commercially available or can be readily produced by known methods.

Each of the reaction products obtained by the aforementioned production methods is isolated and purified as a free compound, a salt thereof, a hydrate thereof or a solvate thereof. The salt can be produced by a usual salt forming method.

The isolation and purification are carried out by optionally employing usually used chemical techniques such as extraction, concentration, evaporation, crystallization, filtration, recrystallization, various types of chromatography and the like.

Various forms of isomers can be isolated by the usual procedures making use of physicochemical difference among isomers. Optical isomers can be isolated by means of a common racemic resolution method such as fractional crystallization or a chromatography. In addition, an optical isomer can also be synthesized from an appropriate optically active starting compound.

[0027]

[Effect of the Invention]

The CRACC inhibitor of the present invention has antiinflammatory and antiallergic activity on the basis of inhibitory activities on CRACC. Therefore, it is useful

for use in the prevention and treatment of inflammatory or allergic diseases in which CRACC is concerned. Examples of these inflammatory or allergic diseases include bronchial asthma, psoriasis, atopic diseases including atopic dermatitis, collagen disease, rheumatoid arthritis, osteoarthritis, inflammatory bowel diseases including Crohn disease, peptic ulcer, glomerular nephritis, hepatitis and pancreatitis.

Anti-proliferative effect of the CRACC inhibitor suggests that it should be useful in preventing or treating proliferative or progressive diseases such as mallignant tumor, arteriosclerosis, multiple organ sclerosis, various types of fibrosis, burn keloid and the like.

[0028]

Further, since the CRACC inhibitor inhibits the IL-2 production in lymphocytes, it is useful in the prevention and treatment of autoimmune diseases and rejection on transplantation.

Also, since the CRACC inhibitor inhibits activation of mast cells, inflammatory cells and astrocytes which concern with inflammation in several peripheral or brain tissues, its action to protect tissues from their damages such as ischemia-reperfusion injury, head injury, cerebral infarction and myocardial infarction can be expected.

In particular, the CRACC inhibitor of the present invention having CRACC selective inhibitory activity over VOCC is useful as an anti-inflammation agent, an anti-allergic agent, an anti-proliferation agent and cell-protection agent, because it can cause CRACC inhibition without VOCC inhibition-induced undesirable reactions in central nerve system and cardiovascular system and the like.

[0029]

The following shows certain tests and their results in order to confirm the CRACC inhibitory activity of the CRACC inhibitor of the present invention.

(Pharmacological test method)

(1) CRACC inhibitory activity evaluation method

Jarkat cells (6×10^5/ml) suspension loaded with a calcium indicator fluorescence dye fura-2 (1 μM) was dispensed in 100 μl portions into wells of a 96 well microplate. Intracellular calcium increase stimulated with a calcium pump inhibitor (thapsigargin) was induced by adding to each well a 100 μl of Hanks' balanced salt solution containing a drug to be tested in two times higher concentration than the final concentration and 2 μM of thapsigargin (final concentration, 1 μM), and, after 30 minutes of the addition, a fluorescence intensity ratio (R) was calculated from two fluorescence intensities obtained

at excitation wave length of 340 nm/500 nm and 380 nm/ 500 nm, respectively. In calculating R, self-fluorescence of the drug to be tested was measured in a cell-free system, and the effect of the self-fluorescence on the fura-2 fluorescence was corrected.

The intracellular calcium concentration was obtained by the following calculation formula on a maximum reaction of R (Rmax) obtained by 25 μM ionomycin stimulation, a minimum reaction of R (Rmin) obtained by 5 μM ionomycin + 1 mM EGTA stimulation, a fluorescence efficiency (Sb2) of a calcium binding dye at an excitation wave length of 380 nm and a fluorescence efficiency (Sf2) of a calcium dissociation dye at an excitation wave length of 380 nm.

Calculation formula:

Intracellular calcium concentration (nM)

$= 224 \times [(R - Rmin)/(Rmax - R)] \times [Sf2/Sb2]$

Using the thus calculated intracellular calcium concentration in the presence of a predetermined concentration of each of the drugs and that of the control solvent, a ratio of inhibiting calcium influx (CRACC inhibition) was obtained to calculate its concentration to inhibit 50% of CRACC (IC_{50} value).

[0030]

(2) VOCC inhibitory activity evaluation method

A suspension of rat neuroblasts PC12-h5 (2 x 10^6/ml) loaded with a calcium indicator fluorescence dye fura-2 (1 μM) was dispensed in 100 μl portions into wells of a 96 well microplate. Intracellular calcium increase stimulated with high concentration potassium chloride was induced by adding to each well a 100 μl of Hanks' balanced salt solution containing a drug to be tested in two times higher concentration than the final concentration and 100 mM of KCl (final concentration, 50 mM), and, after 30 minutes of the addition, a fluorescence intensity ratio (R) was calculated from two fluorescence intensities obtained at excitation wave length of 340 nm/500 nm and 380 nm/ 500 nm, respectively. In calculating R, self-fluorescence of the drug to be tested was measured in a cell-free system, and the effect of the self-fluorescence on the fura-2 fluorescence was corrected.

As in the above-described CRACC inhibition(1), the intracellular calcium influx inhibition of each of the drugs to be tested (VOCC inhibition) was obtained to calculate its concentration to inhibit 50% of VOCC (IC_{50} value).

[0031]

(Results)

The compounds of the present invention had desirable CRACC inhibition activities. Further compounds of the present invention had excellent CRACC inhibition activities over VOCC inhibition activity. Thus, the compounds of the present invention were confirmed to have CRACC selectivity.

CRACC inhibition activities of the compounds of the present invention are shown in the following table. Further, as the index of selectivity of CRACC, the ratio of IC_{50} value with VOCC inhibition activity (VOCC/CRACC) will be shown.

[0032]

[Table 4]

Test compound	CRACC inhibition IC_{50} (μM)	VOCC/CRACC
Example 1	0.27	12
Example 2	0.21	9
Example 39	0.16	7
Example 42	0.35	6
Example 123	0.08	29
Compound B	0.21	21
Compound C	0.27	9
Compound E	0.26	9
Compound F	0.34	7
Compound G	0.20	4
Compound H	0.28	4
Compound J	0.35	7
Compound K	0.17	12
Compound L	0.31	6
Compound M	0.33	6
Compound N	0.26	13
Comparative.comp.		
Compound W	7.7	0.17

Compound W: the compound described in the above-described J. Pharm. Exp. Ther., 257, p967-971 (1991)

[0033]

A medicament comprising the present compound (I) or (I') or a pharmaceutically acceptable salt thereof, as an active ingredient, can be prepared by a usually used method using at least one of compounds represented by the general formula (I) or (I') of the present invention or pharmaceutically acceptable salts thereof and a carrier for medicinal use, an excipient and other additives usually used in pharmaceutical preparations. Its administration may be effected either by oral administration in the form of tablets, pills, capsules, granules, powders, solutions, inhalation and the like or by parenteral administration in the form of intravenous, intramuscular and the like injections, suppositories, eye lotions, eye ointments, transdermal absorption liquid agent, ointment, transdermal plaster, transmucosal liquid agent, and transmucosal plaster.

The solid composition for use in the oral administration according to the present invention is used in the form of tablets, powders, granules and the like. In such a solid composition, one or more active substances are mixed with at least one inert diluent such as lactose, mannitol, glucose, hydoxypropylcellulose, microcrystalline cellulose, starch, polyvinyl pyrrolidone or magnesium aluminate methasilicate. By the usual procedures, the composition may contain other additives than the inert

diluent, such as a lubricant (e.g., magnesium stearate or the like), a disintegrating agent (e.g., calcium cellulose glycolate or the like), a stabilizing agent (e.g., lactose or the like) and a solubilization assisting agent (e.g., glutamic acid, aspartic acid or the like). If necessary, tablets or pills may be coated with films of a sugar or a gastric or enteric substance such as sucrose, gelatin, hydroxypropylcellulose, hydroxypropylmethylcellulose phthalate or the like.

[0034]

The liquid composition for oral administration use includes pharmaceutically acceptable emulsions, solutions, suspensions, syrups, elixirs and the like and contains a generally used inert diluent such as purified water or ethanol. In addition to the inert diluent, this composition may also contain auxiliary agents such as a moistening agent, a suspending agent and the like, as well as sweeteners, flavors, aromatics and antiseptics.

The injections for parenteral administration use include aseptic aqueous or non-aqueous solutions, suspensions and emulsions. Examples of the aqueous solutions and suspensions include distilled water for injection use and physiological saline. Examples of the non-aqueous solutions and suspensions include propylene glycol, polyethylene glycol, plant oil (e.g., olive oil or the like), alcohols (e.g. ethanol and the like), and

Polysorbate 80 (trade name). Such a composition may further contain auxiliary agents such as an antiseptic, a moistening agent, an emulsifying agent, a dispersing agent, a stabilizing agent (lactose for example) and a solubilization assisting agent (glutamic acid or aspartic acid for example). These compositions are sterilized by filtration through a bacteria retaining filter, blending of a germicide or irradiation. Alternatively, they may be used by firstly making into sterile solid compositions and then dissolving them in sterile water or a sterile solvent for injection use prior to their use.

[0035]

A transmucosal agent such as a nasal agent can be solid, liquid or semi-solid, and can be produced by a known method per se. For example, known pH regulator, antiseptics, thickener or shaping agent is optionally added so that the transmucosal agent may be formed in the form of a solid, liquid or semi-solid. The nasal agent can be administered by means of an ordinary spray tool, collunarium container, tube or nasal cavity inserting tool.

In the case of oral administration, suitable daily dose is usually from 0.001 to 30 mg/kg body weight, preferably 0.1 to 5 mg/kg, and the daily dose is administered once a day or divided into 2 to 4 doses per day. In the case of intravenous injection, suitable daily

dose in usually from about 0.001 to 30 mg/kg body weight, and the daily dose is administered once a day or divided into a plurality of doses per day. In the case of nasal administration, suitable daily dose in usually from about 0.001 to 30 mg/kg body weight, and the daily dose is administered once a day or divided into a plurality of doses per day. The dose is optionally decided by taking into consideration symptoms, age, sex and the like of each patient to be treated.

[0036]

[Examples]

The present invention will be described in detail by, but by no means limited to, the following Examples.

In the following Reference Examples and Examples, the following abbreviations are used.

SolA: saturated aqueous sodium bicarbonate solution, SCG: silca gel column chromatography, DrA: anhydrous magnesium sulfate, DrB: anhydrous sodium sulfate

[0037]

Reference Example 1

A mixture of 2-fluoro-5-nitrobenzophenone (3.02 g), sodium methoxide (2.00 g) and methanol (30 ml) was stirred for 1 hour at room temperature. Thereafter, the resulting reaction liquid was concentrated under reduced pressure. The residue was added ethyl acetate (100 ml) and then washed with water, saturated brine in that order. The

organic layer formed was dried with DrB, followed by concentrating under reduced pressure to give a mixture of 2-methoxy-5-nitrobenzophenone and 2-ethoxy-5-nitrobenzophenone (existing ratio = about 4 : 1, 3.01 g) as colorless solid.

[0038]

Reference Example 2

A mixture (2.90 g) of 2-methoxy-5-nitrobenzophenone and 2-ethoxy-5-nitrobenzophenone obtained in Reference Example 1, iron powder (7.00 g), 1N hydrochloric acid (3 ml) and ethanol (30 ml) was stirred under reflux overnight. Thereafter, the resulting mixture was purified by a conventional method to give a mixture of 5-amino-2-methoxybenzophenone and 5-amino-2-ethoxybenzophenone (existing ratio= about 4 : 1, 2.67 g) as brown oily matter.

Reference Example 3

To a mixture of 2,4-dichlorobenzyl alcohol (25.0 g), imidazole (24.5 g), 4-dimethylaminopyridine (86 mg) and DMF (50 ml) was added tert-butyldimethylsilyl chloride (22.2 g) under ice-cooling. The resulting mixture was stirred at room temperature for 26 hours, followed by purification according to a conventional method to give tert-butyldimethylsilyl 2,4-dichlorobenzyl ether (42.0 g) as colorless oily matter.

[0039]

Reference Example 4

To a mixture of tert-butyldimethylsilyl 2,4-dichlorobenzyl ether (33.8 g) and THF (300 ml) was added n-butyl lithium-n-hexane solution (1.60 N, 80.0 ml) at -65°C, which was stirred at -65°C for additional 1 hour under an argon atmosphere. To the resulting reaction mixture was added a mixture of 3,4-dimethoxybenzoyl chloride (28.0 g) and THF (30 ml), which was stirred at -60 to -70°C for 3 hours. Thereafter, 1N hydrochloric acid (12 ml) and concentrated hydrochloric acid (80 ml) were added to the reaction mixture thus obtained, then the resulting mixture was stirred at room temperature for 18 hours, followed by purification according to a conventional method to give 2,6-dichloro-3-hydroxymethyl-3', 4'-dimethoxybenzophenone (17.6 g) as yellow amorphous solid.

Reference Example 5

To a mixture of 2-amino-6-bromo-4-chlorophenol (2.98 g), sodium bicarbonate (2.70 g), 2-butanone (9 ml) and water (9 ml) was added bromoacetyl bromide (1.40 ml) under ice-cooling. The resulting mixture was stirred at room temperature for 1 hour, and further stirred under reflux for 19 hours, followed by purification according to a conventional method to give 8-bromo-6-chloro-3,4-dihydro-2H-1,4-benzoxazine-3-on (1.11g) as pale brown powdery crystals.

[0040]

Reference Example 6

A mixture of 8-bromo-6-chloro-3,4-dihydro-2H-1,4-benzoxazine-3-one(1.10 g), borane-THF complex-THF solution (1.0 M, 13 ml) and THF (20 ml) was stirred under reflux for 21 hours. Then ethanol (10 ml) and 1N hydrochloric acid (15 ml) were added to the reaction mixture thus obtained at room temperature, which was stirred at 80°C for 6 hours. Purification according to a conventional method gave 8-bromo-6-chloro-3,4-dihydro-2H-1,4-benzoxazine hydrochloride (770 mg) as pale red scale crystals.

Reference Example 7

To a mixture of 2-acetylthiophene (18.5 g) and methanol (150 ml) was added sodium methoxide (10.3 g) under ice-cooling, followed by stirring at room temperature for 20 minutes. Then, ethyl trifluoroacetate (25.0 g) was added to the reaction mixture thus obtained under ice-cooling, the mixture was stirred under reflux for 19 hours, followed by purification according to a conventional method to give a pale brown solid (34.7 g). A mixture of this pale brown solid (20.0 g), methyl hydrazine (4.56 g), acetic acid (20 ml) and ethanol (200 ml) was stirred under reflux for 30 minutes, followed by purification according to a conventional method to give 1-methyl-5-(2-thienyl)-3-trifluoromethyl-1H-pyrazole (11.8 g) as yellow oily matter (11.8 g).

[0041]

Compounds of Reference Examples 8 and 9 were obtained as in Reference Example 7.

Reference Example 8

3-(2-thienyl)-5-trifluoromethyl-1H-pyrazole

Reference Example 9

2-[1-methyl-3-trifluoromethyl-1H-pyrazol-5-yl]thiazole

Reference Example 10

A mixture of diisopropylamine (3.34 g) and THF (25 ml) was added with n-butyllithium-n-hexane solution (1.6N, 21 ml) at a temperature of -30°C or less, followed by stirring at -30 to -50°C for 15 minutes. Then, 2-propionyl thiophene (4.21 g) was added to the reaction mixture thus obtained at a temperature of -60°C or less, and the mixture was stirred at -60°C or less for 90 minutes. The resulting reaction mixture was added to a mixture of trifluoroacetic anhydride (31.5 g) and THF (30 ml) cooled to -60°C, which was stirred at -60°C for 1 hour, followed by purification according to a conventional method to give a brown oily matter (1.01 g). A mixture of this brown oily matter (569 mg), hydrazine hydrochloride (181 mg) and ethanol (5 ml) was stirred at 50°C for 2 hours, followed by purification according to a conventional method to give 4-methyl-3-(2-thienyl)-5-trifluoromethyl-1H-pyrazole (448 mg) as brown solid.

[0042]

Reference Example 11

To a mixture of 3-(2-thienyl)-5-trifluoromethyl-1H-pyrazole (5.02 g) and THF (50 ml) was added n-butyllithium-n-hexane solution (1.6 M, 30 ml) at a temperature of -60°C or less, followed by stirring at 0°C for 50 minutes. Then, ethyl chloroformate (4.62 ml) was added to the reaction mixture thus obtained at a temperature of -60°C or less, which was stirred at -78°C for 1 hour, followed by purification according to a conventional method to give pale yellow solid, i.e., a mixture of ethyl 5-(1-ethoxycarbonyl-5-trifluoromethyl-1H-pyrazol-3-yl)-2-thiophenecarboxylate and ethyl 5-(1-ethoxycarbonyl-3-trifluoromethyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate. To this mixture sodium bicarbonate (1.08 g), ethanol (50 ml), 1,4-dioxane (30 ml) and water (20 ml) was added, and the whole was stirred at room temperature for 3 days, followed by purification according to a conventional method to give ethyl 5-(5-trifluoromethyl-1H-pyrazol-3-yl)-2-thiophenecarboxylate (3.48 g) as colorless powdery crystals.

Reference Example 12

n-Butyllithium-n-hexane solution (1.6M, 33 ml) was added to a mixture of 1-methyl-5-(2-thienyl)-3-trifluoromethyl-1H-pyrazole (11.2g) and THF (150 ml) at a temperature of -50°C or less, followed by stirring at -50°C or less for 90 minutes. Then, ethyl chloroformate (10.5 g)

was added to the reaction mixture at a temperature of -20°C or less, which was stirred at -20°C or less for 15 minutes, followed by purification according to a conventional method to give ethyl 5-(1-methyl-3-trifluoromethyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (9.58 g) as pale yellow solid.

[0043]

The compound of Reference Example 13 was obtained as in Reference Example 12.

Reference Example 13

Ethyl 2-(1-methyl-3-trifluoromethyl-1H-pyrazol-5-yl)-5-thiazolecarboxylate

Reference Example 14

A mixture of ethyl 5-(5-trifluoromethyl-1H-pyrazol-3-yl)-2-thiophenecarboxylate (1.01 g), ethyl iodide (0.417 ml), potassium carbonate (481 mg) and DMF (10 ml) were stirred at room temperature for 9 hours. The residue obtained by the ordinary treatment was purified by SCG (eluent: n-hexane : ethyl acetate = 15 : 1) to give ethyl 5-(1-ethyl-5-trifluoromethyl-1H-pyrazol-3-yl)-2-thiophenecarboxylate (665 mg) as colorless needles.

Reference Example 15

In the SCG treatment of Reference Example 14, after having eluted the compound of Reference Example 14, the eluent was changed to n-hexane : ethyl acetate = 10 : 1 to elute ethyl 5-(1-ethyl-3-trifluoromethyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (364mg) as pale yellow oily matter.

[0044]

The compounds of Reference Examples 16 and 17 were obtained as in Reference Examples 14 and 15.

Reference Example 16

Ethyl 5-(1-isopropyl-5-trifluoromethyl-1H-pyrazol-3-yl)-2-thiophenecarboxylate

Reference Example 17

Ethyl 5-(1-isopropyl-3-trifluoromethyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate

Reference Example 18

4-methyl-3-(2-thienyl)-5-trifluoromethyl-1H-pyrazole (1.53 g) was reacted with n-butyllithium-n-hexane solution (1.6 M, 9 ml). Then, to the resulting reaction mixture was added ethyl chloroformate (1.79 g) at a temperature of -50°C or less, which was stirred at -50°C or less for 30 minutes, followed by purification according to a conventional method to give yellow oily matter. A mixture of this yellow oily matter, 5N aqueous sodium hydroxide solution (10 ml) and ethanol (20 ml) was stirred at room temperature overnight, followed by purification according to a conventional method to give 5-(4-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-2-thiophenecarboxylic acid (1.04 g) as colorless powdery crystals.

[0045]

Reference Example 19

A mixture of ethyl 5-(1-ethyl-5-trifluoromethyl-1H-pyrazol-3-yl)-2-thiophenecarboxylate (632 mg), 5N aqueous sodium hydroxide solution (1 ml), ethanol (5 ml) and 1,4-dioxane (1 ml) was stirred at room temperature for 20 hours, followed by purification according to a conventional method to give 5-(1-ethyl-5-trifluoromethyl-1H-pyrazol-3-yl)-2-thiophenecarboxylic acid (425 mg) as colorless powdery crystals.

The compounds of Reference Examples 20 to 25 were obtained as in Reference Example 19.

Reference Example 20

5-(1-ethyl-3-trifluoromethyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid

Reference Example 21

5-(1-isopropyl-5-trifluoromethyl-1H-pyrazol-3-yl)-2-thiophenecarboxylic acid

Reference Example 22

5-(1-isopropyl-3-trifluoromethyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid

Reference Example 23

5-(5-trifluoromethyl-1H-pyrazol-3-yl)-2-thiophenecarboxylic acid

Reference Example 24

5-(1-methyl-3-trifluoromethyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid

Reference Example 25

2-(1-methyl-3-trifluoromethyl-1H-pyrazol-5-yl)-5-thiazolecarboxylic acid

[0046]

Reference Example 26

2-(2-thienyl)-4-trifluoromethylthiazole (1.00 g) and n-butyllithium-n-hexane solution (1.6 M, 2.9 ml) were stirred at -40°C or less in THF. Then, to the resulting reaction mixture was added tert-butyldimethylsilyl chloride (960 mg) at a temperature of -70°C or less, which was stirred at room temperature for 4 hours, followed by purification according to a conventional method to give 5-tert-butyldimethylsilyl-2-(2-thienyl)-4-trifluoromethylthiazole (1.02 g) as yellow oily matter.

Reference Example 27

5-tert-butyldimethylsilyl-2-(2-thienyl)-4-trifluoromethylthiazole (1.05 g) was reacted with n-butyl lithium-n-hexane solution (1.6 M, 2.1 ml) in THF at -40°C or less. Then, to the resulting reaction mixture was added ethyl chloroformate (0.43 ml) at a temperature of -70°C or less, which was stirred at 0°C for 1 hour, followed by purification according to a conventional method to give yellow oily matter (1.32 g). A mixture of this yellow oily

matter (1.20 g) and ethanol (15 ml) was added with 1N aqueous sodium hydroxide solution (10 ml) and 1,4-dioxane (10 ml), followed by stirring at room temperature for 7 hours. Purification according to a conventional method gave 5-(4-trifluoromethyl-2-thiazolyl)-2-thiophenecarboxylic acid (303 mg) as pale yellow solid.

Reference Example 28

A mixture of 5-(1-methyl-3-trifluoromethyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (2.21 g), oxalyl chloride (2.03 g), DMF (three drops) and 1,2-dichloroethane (30 ml) was stirred at room temperature for 90 minutes, followed by purification according to a conventional method to give 5-(1-methyl-3-trifluoromethyl-1H-pyrazol-5-yl)-2-thiophenecarbonyl chloride (2.23 g) as brown solid.

[0047]

Reference Example 29

A mixture of 5-(1-methyl-3-trifluoromethyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (905 mg),. diphenyl phosphoryl azide, triethylamine and toluene was stirred at 50°C for 30 minutes. To the resulting reaction mixture, tert-butanol (486 mg) was further added and the mixture obtained was stirred at 80°C for 5 hours, followed by purification according to a conventional method to give tert-butyl 5-(1-methyl-3-trifluoromethyl-1H-pyrazol-5-yl)-2-thiophenecarbamate (223 mg) as pale yellow crystals.

Reference Example 30

A mixture of tert-butyl 5-(1-methyl-3-trifluoromethyl-1H-pyrazol-5-yl)-2-thiophenecarbamate (223 mg), trifluoroacetic acid (5 ml) and dichloromethane (5 ml) was stirred at room temperature for 2 days, followed by purification according to a conventional method to give 5-(5-amino-2-thienyl)-1-methyl-3-trifluoromethyl-1H-pyrazole hydrochloride (154 mg) as pale yellow powdery crystals.

[0048]

Reference Example 31

To an aqueous ethanol solution of 1-(4-nitrophenyl)-3,5-bis(trifluoromethyl)-1H-pyrazole (5.10 g) were added zinc powder (10.3 g) and ammonium chloride (8.4 g) under ice-cooling, followed by stirring at 20°C for 30 minutes. Then insoluble matters in the reaction mixture was removed by Celite filtration and the filtrate obtained was treated according to a conventional method, whereby crude 1-(4-hydroxyaminophenyl)-3,5-bis(trifluoromethyl)-1H-pyrazole (5.01 g) was obtained as colorless solid.

Reference Example 32

To a mixture of 5-(1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-2-thiophenecarboxyaldehyde (1.00 g), silver nitrate powder (1.37 g) and ethanol was added a mixture of 5N aqueous sodium hydroxide solution (5 ml) and ethanol under ice-cooling. The resulting mixture was stirred at room temperature for 1 hour, followed by purification

according to a conventional method to give 5-(1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-2-thiophenecarboxylic acid (974 mg) as colorless powder.

[0049]

Example 1 (Production of a known compound)

A mixture of 3-bromo-5-chlorosalicylic acid (2.09 g), 5-amino-2-chlorobenzophenone (1.83 g), WSCD hydrochloride (1.82 g) and THF (20 ml) was stirred at room temperature for 4 days. Ethyl acetate (200 ml) was added to a reaction mixture. Successively, the mixture obtained was washed with water, SolA, saturated brine, 1N hydrochloric acid and saturated brine in that order. The organic phase formed was dried over DrB, thereafter the dried organic phase was concentrated under reduced pressure. The residue obtained was purified by SCG (eluent: n-hexane : ethyl acetate = 6 : 1) and recrystallized from a mixed solvent of ethyl acetate and n-hexane to give 3'-benzoyl-3-bromo-4',5-dichloro-2-hydroxybenzanilide (1.53 g) as colorless needles.

Example 2

A mixture of 3-bromo-5-chlorosalicylic acid (500 mg), thionyl chloride (3 ml), dichloroethane (10 ml) and DMF (1 drop) was stirred at 75°C for 2 hours. Successively, the reaction mixture obtained was concentrated under reduced pressure. To the resulting residue were added 3-aminobenzophenone (392 mg), triethylamine (0.277 ml) and 1,2-dichloroethane (10 ml). The reaction mixture thus

obtained was stirred at 75°C for 2 hours and further stirred at room temperature overnight. Then, chloroform was added to the reaction mixture and the resulting mixture was washed with 1N hydrochloric acid, SolA and saturated brine in that order. The organic phase formed was dried over DrB, then concentrated under reduced pressure. Thereafter, the residue obtained was purified by SCG (eluent: n-hexane : ethyl acetate = 4 : 1) and recrystallized from a mixed solvent of ethyl acetate and n-hexane to give 3'-benzoyl-3-bromo-5-chloro-2-hydroxybenzanilide (202 mg) as colorless powdery crystals.

[0050]

Example 3

To a mixture of 5-amino-2-chlorobenzophenone (409 mg), triethylamine (0.370 ml) and THF (5 ml) were added 3,5-dichlorobenzoyl chloride (0.388 ml) and THF (4 ml) under ice-cooling. Then the resulting mixture was stirred at room temperature overnight. Then water was added thereto. Successively, the product obtained was extracted with ethyl acetate. Then, the extract obtained was washed with SolA and saturated brine in that order. The organic phase formed was dried over DrB, thereafter the dried organic phase was concentrated under reduced pressure. The residue obtained was purified by SCG (eluent: n-hexane : ethyl acetate = 8 : 1 ~ 1 : 1) and recrystallized from

ethanol to give 3'-benzoyl-3,4',5-trichlorobenzanilide (391 mg) as colorless needles.

Example 4

To a mixture of 5-amino-2-chlorobenzophenone (370 mg), triethylamine (0.335 ml) and THF (5 ml) were added 2-acetoxybenzoyl chloride (351 mg) and THF (3 ml) under ice-cooling. Then the resulting mixture was stirred at room temperature for 2 hours and 30 minutes. SolA was further added to the resulting reaction mixture and stirred at room temperature overnight. Successively, the product obtained was extracted with ethyl acetate. Then, the extract obtained was washed with SolA and saturated brine in that order. The organic phase formed was dried over DrB, thereafter the dried organic phase was concentrated under reduced pressure. The residue obtained was purified by SCG (eluent: n-hexane : ethyl acetate = 16 : 1 ~ 3 : 1) to give 3'-benzoyl-4'-chloro-2-hydroxybenzanilide (40 mg) as yellow amorphous solid.

[0051]

Example 5

In the SCG treatment of Example 4, 2-acetoxy-3'-benzoyl-4'-chlorobenzanilide (368 mg) eluted after the compound of Example 4 was obtained as colorless amorphous solid.

Example 6

A mixture of 3'-benzoyl-3-bromo-4',5-dichloro-2-hydroxybenzanilide (150 mg), acetyl chloride (0.024 ml), triethylamine (0.049 ml) and 2-butanone (4 ml) was stirred at room temperature for 2 days. Then water was added thereto. Successively, the product obtained was extracted with ethyl acetate. Then, the extract obtained was washed with saturated brine. The organic phase formed was dried over DrB, thereafter the dried organic phase was concentrated under reduced pressure. The residue obtained was purified by SCG (eluent: n-hexane : ethyl acetate = 16 : 1 ~ 4 : 1) to give 2-acetoxy-N-acetyl-3'-benzoyl-3-bromo-4',5-dichlorobenzanilide 0.75 hydrate (105 mg) as colorless amorphous solid.

[0052]

Example 7

In the SCG treatment of Example 6, 2-acetoxy-3'-benzoyl-3-bromo-4',5-dichlorobenzanilide (25 mg) eluted after the compound of Example 6 was obtained as colorless amorphous solid.

Example 8

A mixture of 3'-benzoyl-3-bromo-4',5-dichloro-2-hydroxybenzanilide (150 mg), methyl iodide (0.200 ml), potassium carbonate (178 mg) and 2-butanone (4 ml) was stirred at room temperature overnight. Potassium carbonate (178 mg) was further added thereto and the resulting

mixture was further stirred at room temperature overnight. Then water was added to the resulting reaction mixture and, successively, the product obtained was extracted with ethyl acetate. Thereafter, the extract obtained was washed with saturated brine. The organic phase formed was dried over DrB, thereafter the dried organic phase was concentrated under reduced pressure. The residue obtained was purified by SCG (eluent: n-hexane : ethyl acetate = 16 : 1 ~ 4 : 1) to give 3'-benzoyl-3-bromo-4',5-dichloro-2-methoxy-N-methylbenzanilide (127 mg) as colorless amorphous solid.

[0053]

Example 9

A mixture of 3-bromo-5-chlorosalicylic acid (500 mg), thionyl chloride (0.218 ml), 1,2-dichloroethane (10 ml) and DMF (0.008 ml) was stirred at 75°C for 1.5 hours. Successively, the reaction mixture obtained was concentrated under reduced pressure. To the resulting residue were added a mixture (452 mg) of 5-amino-2-methoxybenzophenone and 5-amino-2-ethoxybenzophenone obtained in Reference Example 2, triethylamine (0.333 ml) and 1,2-dichloroethane (12 ml). The reaction mixture thus obtained was stirred at room temperature overnight. Then, water and 1N hydrochloric acid were added to the resulting reaction mixture. Successively, the resulting product was extracted with ethyl acetate and the extract thus obtained was washed with SolA and saturated brine in that order.

The organic phase formed was dried over DrB, and concentrated under reduced pressure, thereafter the residue obtained was purified by SCG (eluent: n-hexane : ethyl acetate = 16 : 1 ~ 4 : 1) and then washed with diethyl ether to give 3'-benzoyl-3-bromo-5-chloro-4'-ethoxybenzanilide (44 mg) as colorless powdery crystals.

Example 10

In the SCG treatment of Example 9, the compound eluted after the compound of Example 9 was recrystallized from a mixed solvent of ethyl acetate, diethyl ether and n-hexane to give 3'-benzoyl-3-bromo-5-chloro-4'-methoxybenzanilide (67 mg) as colorless powdery crystals.

[0054]

Example 11

To a mixture of 3-bromo-5-chlorosalicylic acid (500 mg), triphenylphosphine (574 mg), NBS (390 mg) and dichloromethane (20 ml) were added 5-amino-2-fluorobenzophenone (514 mg) and dichloromethane under ice-cooling. The resulting mixture was stirred at room temperature for 30 minutes. Then, water was added to the resulting reaction mixture and, successively, the product obtained was extracted with ethyl acetate. Thereafter, the extract obtained was washed with SolA, 1N hydrochloric acid and saturated brine in that order. The organic phase formed was dried over DrB, thereafter the dried organic phase was concentrated under reduced pressure. The residue

obtained was purified by SCG (eluent: n-hexane : ethyl acetate = 16 : 1 ~ 4 : 1) and then recrystallized from a mixed solvent of ethyl acetate, diethyl ether and n-hexane to give 3'-benzoyl-3-bromo-5-chloro-4'-fluoro-2-hydroxybenzanilide (122 mg) as yellow powdery crystals.

Example 12

In the SCG treatment of Example 17, the compound eluted after the compound of Example 17 was crystallized from n-hexane, and successively recrystallized from a mixed solvent of ethyl acetate and n-hexane to give 2-amino-3'-benzoyl-4',5-dichlorobenzanilide (28 mg) as colorless powdery crystals.

[0055]

Example 13

A mixture of 3-bromo-5-chlorosalicylaldehyde (341 mg), 5-amino-2-chlorobenzophenone (310 mg) and ethanol (6 ml) was stirred under reflux for 1 hour. The resulting reaction mixture was concentrated under pressure to give residue to which sodium triacetoxyborohydride (298 mg), acetic acid (5 ml) and dichloroethane (125 ml) were added. The resulting mixture was stirred at 0°C overnight. Then ethyl acetate (350 ml) was added to the reaction mixture and washed with SolA and saturated brine in that order. The organic phase formed was dried over DrB, thereafter the dried organic phase was concentrated under reduced pressure. The residue obtained was purified by SCG

(eluent: n-hexane : ethyl acetate = 10 : 1 ~ 2 : 1) to give 5-[(3-bromo-5-chloro-2-hydroxybenzyl)amino]-2-chlorobenzophenone (355 mg) as yellow oily crystals.

Example 14

A mixture of 3-bromo-5-chlorosalicylic acid (250 mg), 4-aminobenzophenone (200 mg), phosphorus trichloride (0.087 ml) and chlorobenzene (5 ml) was stirred under reflux for 3 hours. Then water was added to the reaction mixture and the resulting product was extracted with ethyl acetate. Thereafter, the extract obtained was washed with SolA, 1N hydrochloric acid and saturated brine in that order. The organic phase formed was dried over DrB, thereafter the dried organic phase was concentrated under reduced pressure. The residue obtained was crystallized from a mixed solvent of 2-propanol and diethyl ether, and successively recrystallized from ethyl acetate to give 4'-benzoyl-3-bromo-5-chloro-2-hydroxybenzanilide (46 mg) as yellow needles.

[0056]

Example 15

To a mixture of imidazo[1,2-a]pyridine-3-carboxylic acid (65 mg), 4-amino-3,4',5-trichlorobenzophenone (121 mg) and pyridine (1.2 ml) was added phosphorus oxychloride (0.059 ml) at a temperature of -10°C or less, which was stirred at -15°C for 90 minutes. Then ice was added to the reaction mixture and the resulting product was extracted

with ethyl acetate. Thereafter, the extract obtained was washed with saturated brine. The organic phase formed was dried over DrB, thereafter the dried organic phase was concentrated under reduced pressure. The residue obtained was purified by SCG (eluent: chloroform: methanol = 49 : 1) and recrystallized from a mixed-solvent of ethyl acetate and n-hexane to give N-[4-(4-chlorobenzoyl)-3,5-dichlorophenyl]imidazo[1,2-a]pyridine-3-carboxyamide (27 mg) as pale brown powdery crystals.

Example 16

A mixture of triphenylphosphine (1.15 g), bromine (0.199 ml) and dichloromethane (300 ml) was stirred at room temperature for 15 minutes in an argon atmosphere. To the resulting reaction mixture was added a mixture of 2,6-dichloro-3-hydroxymethyl-3',4'-dimethoxybenzophenone (1.20 g) and dichlormethane (15 ml), which was stirred at room temperature for 18 hours. The reaction mixture was concentrated under reduced pressure to give crude 3-bromomethyl-2,6-dichloro-3',4'-dimethoxybenzophenone (3.00 g) as yellow oily matter.

To a mixture of 8-bromo-6-chloro-3,4-dihydro-2H-1,4-benzoxazine (676 mg) and DMF (3 ml) was added 60% sodium hydrazide (109 mg) under ice-cooling. The resulting mixture was stirred at room temperature for 20 minutes. Thereafter, to the resulting reaction mixture was added a mixture of the previously prepared crude 3-bromomethyl-2,6-

dichloro-3',4'-dimethoxybenzophenone (3.00 g) and DMF (3 ml), which was stirred at room temperature for 4 days. Then water (100 ml) was added to the resulting reaction mixture and, successively, the product obtained was extracted with ethyl acetate. Thereafter, the extract obtained was washed with water and saturated brine in that order. The organic phase formed was dried over DrB, thereafter the dried organic phase was concentrated under reduced pressure. The residue obtained was purified by SCG (eluent: n-hexane : ethyl acetate = 10 : 1 ~ 3 : 1) and then recrystallized from a mixed solvent of acetonitrile and chloroform to give 3-[(8-bromo-6-chloro-3,4-dihydro-2H-1,4-benzoxazin-4-yl)methyl]-2,6-dichloro-3',4'-dimethoxybenzophenone (575 mg) as colorless powdery crystals.

[0057]

Example 17

A mixture of 4-chlorophthalic anhydride (3.00 g), trimethylsilylazide (8.75 ml) and acetonitrile (100 ml) was stirred under reflux for 4 hours. Then water was added to the resulting reaction mixture and, successively, the product obtained was extracted with ethyl acetate. Thereafter, the extract obtained was dried over DrB, thereafter concentrated under reduced pressure. To the residue obtained was added 5-amino-2-chlorobenzophenone (3.82 g) and toluene (200 ml), which was stirred under

reflux for 4 hours and 30 minutes. The formed precipitate was filtered off and the filtrate obtained was concentrated under reduced pressure. Then the resulting residue was purified by SCG (eluent: n-hexane : ethyl acetate = 5 : 1) and then crystallized from diethyl ether and then recrystallized from a mixed solvent of ethyl acetate and n-hexane to give 2-amino-3'-benzoyl-4,4'-dichlorobenzanilide (164 mg) as colorless powdery crystals.

Example 18

A mixture of 2-amino-3'-benzoyl-4,4'-dichlorobenzanilide (130 mg), acetic anhydride (0.060 ml) and pyridine (5 ml) was stirred at room temperature for 23 hours. Then ethyl acetate was added to the reaction mixture and washed with water, SolA, 1N hydrochloric acid and saturated brine in that order. The organic phase formed was dried over DrB, thereafter the dried organic phase was concentrated under reduced pressure. The residue obtained was purified by SCG (eluent: n-hexane : ethyl acetate = 9 : 1 ~ 7 : 3) and then recrystallized from a mixed solvent of ethyl acetate and n-hexane to give 2-acetamide-3'-benzoyl-4,4'-dichlorobenzanilide (59 mg) as colorless powdery crystals.

[0058]

Example 19

A mixture of 4'-chloro-5-(5-trifluoromethyl-1H-pyrazol-3-yl)-2-thenanilide (163 mg), benzylbromide (0.057

ml), potassium carbonate (61 mg) and DMF (2 ml) was stirred at room temperature for 20 hours. Then ethyl acetate (50 ml) was added to the reaction mixture and washed with water and saturated brine in that order. The organic phase formed was dried over DrB, thereafter the dried organic phase was concentrated under reduced pressure. The residue obtained was purified by SCG (eluent: n-hexane : ethyl acetate = 4 : 1) and then recrystallized from a mixed solvent of ethyl acetate and n-hexane to give 5-(1-benzyl-5-trifluoromethyl-1H-pyrazol-3-yl)-4'-chloro-2-thenanilide (54 mg) as colorless powdery crystals.

Example 20

In the SCG treatment of Example 19, the compound eluted after the compound of Example 19 was recrystallized from a mixed solvent of ethyl acetate and hexane to give 5-(1-benzyl-3-trifluoromethyl-1H-pyrazol-5-yl)-4'-chloro-2-thenanilide (7 mg) as colorless powdery crystals.

[0059]

Example 21

To a mixture of 2-chloroaniline (68 mg), pyridine (42 mg) and dichloromethane (2 ml) were added 5-(1-methyl-3 -trifluoromethyl-1H-pyrazol-5-yl)-2-thiophenecarbonyl chloride (150 mg) and dichloromethane (1.5 ml). The resulting mixture was stirred at room temperature for 30 minutes. Then, SolA was added to the reaction mixture and the resulting product was extracted with ethyl acetate.

Thereafter, the extract obtained was washed with saturated brine. The organic phase formed was dried over DrA, thereafter the dried organic phase was concentrated under reduced pressure. The residue obtained was recrystallized from ethanol to give 2'-chloro-5-(1-methyl-3-trifluoromethyl-1H-pyrazol-5-yl)-2-thenanilide (80 mg) as colorless crystals.

Example 22

To a mixture of 2-amino-1-methylpyrrole hydrochloride (202 mg), potassium carbonate (553 mg), THF (2 ml) and water (4 ml) were added 5-(1-methyl-3-trifluoromethyl-1H-pyrazol-5-yl)-2-thiophenecarbonyl chloride (295 mg) and THF (3 ml). Then the resulting mixture was stirred at room temperature for 30 minutes. Next, water was added to the reaction mixture thus obtained and the resulting product was extracted with ethyl acetate. Thereafter, the extract obtained was washed with 1N hydrochloric acid, SolA and water in that order. The organic phase formed was dried over DrA, thereafter the dried organic phase was concentrated under reduced pressure. The residue obtained was purified by SCG (eluent: n-hexane : ethyl acetate = 2 : 1 ~ 3 : 2) and then recrystallized from a mixed solvent of ethyl acetate and n-hexane to give N-(1-methyl-2-pyrrolyl)-5-(1-methyl-3-trifluoromethyl-1H-pyrazol-5-yl)-2-thenamide (126 mg) as pale yellow powdery crystals.

[0060]

Example 23

To a mixture of 4-aminopyridine (80 mg), SolA (10 ml) and dichloromethane (2 ml) were added 5-(1-methyl-3-trifluoromethyl-1H-pyrazol-5-yl)-2-thiophenecarbonyl chloride (203 mg) and dichloromethane (10 ml). Then the resulting mixture was stirred at room temperature for 29 hours . Next, ethyl acetate (50 ml) was added to the reaction mixture thus obtained and washed with SolA and saturated brine in that order. The organic phase formed was dried over DrB, thereafter the dried organic phase was concentrated under reduced pressure. The residue obtained was added with ethyl acetate (30 ml) and 4N-hydrochloric acid-1,4-dioxane solution (0.25 ml), which was concentrated under reduced pressure. The resulting pale purple solid was recrystallized from methanol to give 5-(1-methyl-3-trifluoromethyl-1H-pyrazol-5-yl)-N-(4-pyridyl)-2-thenamide hydrochloride (59 mg) as pale purple powdery crystals.

Example 24

To a mixture of 70% aqueous ethylamine solution (1 ml) and THF (2 ml) were added 5-(1-methyl-3-trifluoromethyl-1H-pyrazol-5-yl)-2-thiophenecarbonyl chloride (150 mg) and THF (2 ml). Then the resulting mixture was stirred at room temperature for 2 hours. Next, water was added to the reaction mixture thus obtained and the resulting product was extracted with ethyl acetate.

Thereafter, the extract was washed with saturated brine. The organic phase formed was dried over DrA, thereafter the dried organic phase was concentrated under reduced pressure. The residue obtained was recrystallized from a mixed solvent of ethyl acetate and n-hexane to give N-ethyl-5-(1-methyl-3-trifluoromethyl-1H-pyrazol-5-yl)-2-thenamide (96 mg) as colorless powdery crystals.

[0061]

Example 25

To a mixture of 2-aminothiazole (68 mg), SolA (1 ml) and dichloromethane (1 ml) were added 5-(1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-2-thiophenecarbonyl chloride (100 mg) and dichloromethane (2 ml). Then the resulting mixture was stirred at room temperature for 5 hours. Next, water was added to the reaction mixture thus obtained and the resulting product was extracted with ethyl acetate. Thereafter, the extract was washed with saturated brine. The organic phase formed was dried over DrA, thereafter the dried organic phase was concentrated under reduced pressure. The residue obtained was purified by SCG (eluent: n-hexane : ethyl acetate = 4 : 1 ~ 2 : 1) and then washed with diethyl ether to give 5-(1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-N-(2-thiazolyl)-2-thenamide (68 mg) as colorless solid.

Example 26

A mixture of 3'-acetyl-4-chlorobenzaldehyde (1.00 g) and methanol (10 ml) was added with sodium methoxide (257 mg) under ice-cooling. Then, the resulting mixture was stirred at room temperature for 2 hours. Next, to the resulting reaction mixture was added ethyl trifluoroacetate (0.522 ml) under ice-cooling, followed by stirring for 3 days under reflux with heating. Then water (50 ml) was added thereto and the resulting product was extracted with ethyl acetate. Thereafter, the extract obtained was washed with saturated brine. The organic phase formed was dried over DrB, thereafter the dried organic phase was concentrated under reduced pressure. The residue obtained was purified by SCG (eluent: n-hexane : ethyl acetate = 2 : 1 ~ 1 : 1) to give pale yellow oily matter. A mixture of this yellow oily matter, methyl hydrazine (0.122 ml), acetic acid (1 ml) and ethanol (10 ml) was stirred for 15 hours under reflux. The resulting reaction mixture was allowed to stand for cooling and successively concentrated under reduced pressure. The residue obtained was added with ethyl acetate and washed with SolA and saturated brine in that order. The organic phase formed was dried over DrB, thereafter the dried organic phase was concentrated under reduced pressure. The residue obtained was purified by SCG (eluent: n-hexane : ethyl acetate = 6 : 1) and then recrystallized from a mixed solvent of ethyl acetate and n-

hexane to give 4-chloro-3'-(1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)benzanilide (60 mg) as colorless powdery crystals.

[0062]

Example 27

In the SCG treatment of Example 26, the compound eluted after the compound of Example 26 was recrystallized from a mixed solvent of ethyl acetate and hexane to give 4-chloro-3'-(1-methyl-3-trifluoromethyl-1H-pyrazol-5-yl)benzanilide (134 mg) as colorless powdery crystals.

Example 28

To a mixture of 3-aminopyrazole (125 mg), SolA (10 ml) and dichloromethane (2 ml) were added 5-(1-methyl-3-trifluoromethyl-1H-pyrazol-5-yl)-2-thiophenecarbonyl chloride (250 mg) and dichloromethane (10 ml). Then the resulting mixture was stirred at room temperature for 18 hours. Next, chloroform (30 ml) was added to the reaction mixture and then washed with saturated brine. The organic layer formed was dried over DrB, thereafter the dried organic phase was concentrated under reduced pressure. The residue obtained was purified by SCG (eluent: n-hexane : ethyl acetate = 9 : 1 ~ 1 : 1) and then recrystallized from a mixed solvent of ethyl acetate and hexane to give 5-amino-1-[5-(1-methyl-3-trifluoromethyl-1H-pyrazol-5-yl)-2-thenoyl]-1H-pyrazole (72 mg) as yellow needles.

[0063]

Example 29

In the SCG treatment of Example 28, the compound eluted after the compound of Example 28 was recrystallized from a mixed solvent of ethyl acetate and hexane to give 3-amino-1-[5-(1-methyl-3-trifluoromethyl-1H-pyrazol-5-yl)-2-thenoyl]-1H-pyrazole (28 mg) as pale yellow powdery crystals.

Compounds of Examples 30 to 137 shown in the following Table were produced using appropriate starting materials according to the treatments as in the above-described Examples described in the column of production method of the Table.

Physicochemical properties of the compounds of the above-described Reference Examples which are references of the compounds of the present invention will be shown in Tables 5 and 6 as well as structures and physicochemical properties of the compounds of the above-described Examples will be shown in Tables 7 to 24. In the Tables, each symbol has the following meaning;

Rf.: Reference Example No. Ex.: Example No. Sy: Production method (previous Example No. according to a similar treatment) Str: Structural formula Dat: Physicochemical properties Sal: Salt mp: Melting point dec: Decomposition NMR: Nuclear magnetic resonance spectrum (unless otherwise specified DMSO-d6, TMS internal

standard) δ m/z: Mass analytical data (m/z) Anal: Elemental analytical data calcd: calculated data found: actually measured value Ac: acetyl group

[0064]

[Table 5]

Rf.	Dat
1	m/z: 257(GC-EI,M+), 271(GC-EI,M+) NMR(CDCl3) 1.17(t, OCH2CH3):3.86(s, OCH3)=about4:1 (integration ratio)
2	m/z: 227(GC-EI,M+), 241(GC-EI,M+) NMR(CDCl3) 0.99(t, OCH2CH3):3.64(s, OCH3)=about4:1 (integration ratio)
3	NMR:0.11(6H,s),0.94(9H,s),4.72(2H,s),7.24(1H,dd,J=8.0,2.0Hz),7.30(1H,d,J=2.0Hz), 7.48(1H,d,J=8.0Hz).
4	NMR:2.38(1H,t,J=6.0Hz),3.94(3H,s),3.96(3H,s),4.73-4.82(2H,m,),6.84(1H,d,J=8.0Hz) ,7.16(1H,dd,J=8.0,2.0Hz),7.40(1H,d,J=8.0Hz),7.58(1H,d,J=8.0Hz),7.63(1H,d,J=2 .0Hz).
5	NMR:4.72(2H,s),6.90(1H,d,J=2.4Hz),7.30(1H,d,J=2.4Hz),10.96(1H,brs).
6	NMR:3.28-3.32(2H,m), 4.16-4.21(2H,m), 6.60(1H,d,J=2.7Hz), 6.73(1H,d,J=2.1Hz)
7	NMR(CDCl3): 4.01(3H, s), 6.64(1H, s), 7.15(1H, dd, J=5.2, 3.7Hz), 7.21(1H, dd, J=3.7, 1.3Hz), 7.47(1H, dd, J=5.2, 1.3Hz)
8	NMR(CDCl3): 6.72(1H, s), 7.10-7.15(1H, m), 7.30(1H, dd, J=4.1, 1.1Hz), 7.38-7.42(1H, m), 10.66(br)
9	NMR(CDCl3): 4.32(3H,s), 6.90(1H, s), 7.45(1H, d, J=3.3Hz), 7.93(1H, d, J=3.0Hz)
10	NMR(CDCl3): 2.29(3H, s), 7.16(1H, dd, J=5.2, 3.7Hz), 7.25(1H, dd, J=4.0, 1.0Hz), 7.44(1H, dd, J=5.4, 1.0Hz), 10.86(1H, brs)
11	NMR(CDCl3): 1.40(3H,t,J=7.1Hz), 4.39(2H,q,J=7.1Hz), 6.79(1H,s), 7.28(1H,d,J=4.2Hz), 7.76(1H,d,J=4.2Hz), 11.46(1H,brs)
12	NMR(CDCl3): 1.40(3H, t, J=7.3Hz), 4.05(3H, s), 4.39(2H, q, J=7.0Hz), 6.71(1H, s), 7.20(1H, d, J=4.5Hz), 7.80(1H, d, J=3.5Hz)
13	NMR(CDCl3): 1.41(3H, t, J=7.2Hz), 4.33(3H, s), 4.41(2H, q, J=7.2Hz), 6.97(1H, s), 8.44(1H,s)
14	NMR(CDCl3): 1.38(3H,t,J=7.2Hz), 1.52(3H,t,J=7.4Hz), 4.30(2H,q,J=7.2Hz), 4.36(2H,q,J=6.9Hz), 6.81(1H,s), 7.27-7.30(1H,m), 7.72-7.75(1H,m)
15	NMR(CDCl3): 1.40(3H,t,J=7.2Hz), 1.50(3H,t,J=7.2Hz), 4.31-4.43(4H,m), 6.67(1H, s), 7.16-7.18(1H,m), 7.78-7.81(1H,m)
16	NMR(CDCl3): 1.38(3H,t,J=7.1Hz), 1.56(6H,d,J=6.8Hz), 4.36(2H,q,J=7.2Hz), 4.58-4.69(1H,m), 6.78(1H,s), 7.29(1H,d,J=3.9Hz), 7.73(1H,d,J=3.9Hz)
17	NMR(CDCl3): 1.40(3H,t,J=7.1Hz), 1.53(6H,d,J=6.8Hz), 4.39(2H,q,J=7.0Hz), 4.71-4.82(1H,m), 6.62(1H,s), 7.14(1H,d,J=3.9Hz), 7.80(1H,d,J=3.5Hz)

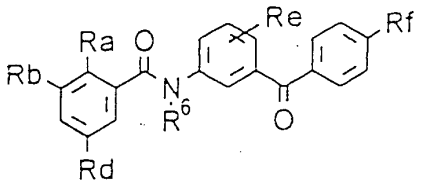
[0065]

[Table 6]

Rf.	Dat
18	NMR: 2.28(3H, s), 7.53(1H, d, J=3.9Hz), 7.81(1H, d, J=3.9Hz), 13.53(1H, brs), 14.11(1H, brs)
19	NMR: 1.42(3H,t,J=7.1Hz), 4.30(2H,q,J=7.2Hz), 7.46(1H,s), 7.58(1H,d,J=3.9Hz), 7.71(1H,d,J=3.6Hz), 13.18(1H,brs)
20	NMR: 1.39(3H,t,J=7.2Hz), 4.37(2H,q,J=7.2Hz), 7.15(1H,s), 7.53(1H,d,J=3.9Hz), 7.80(1H,d,J=3.9Hz), 13.46(1H,brs)
21	NMR: 1.49(6H,d,J=6.8Hz), 4.57-4.68(1H,m), 7.32(1H,s), 7.47(1H,d,J=3.9Hz), 7.50(1H,d,J=3.9Hz)
22	NMR: 1.44(6H,d,J=6.9Hz), 4.77-4.88(1H,m), 7.08(1H,s), 7.48(1H,d,J=3.9Hz), 7.80(1H,d,J=3.6Hz)
23	NMR: 7.07(1H,s), 7.60(1H,d,J=3.7Hz), 7.76(1H,d,J=3.7Hz), 14.42(1H,brs)
24	NMR: 4.06(3H, s), 7.18(1H, s), 7.59(1H, d, J=3.9Hz), 7.80(1H, d, J=3.9Hz), 13.44(1H, brs)
25	NMR: 4.26(3H, s), 7.56(1H, s), 8.52(1H, s)
26	NMR($CDCl_3$):0.40(s, 3H), 0.40(s, 3H), 0.95(s, 9H), 7.09(1H, dd, J=4.8, 4.0Hz), 7.45(1H, dd, J=4.8, 1.4Hz), 7.57(1H, dd, J=3.6, 1.4Hz)
27	NMR($CDCl_3$):7.76(1H, d, J=3.9Hz), 7.86(1H, d, J=3.9Hz), 8.60(1H, s), 13.56(1H, brs)
28	NMR($CDCl_3$): 4.09(3H, s), 6.78(1H, s), 7.30(1H, d, J=4.4Hz), 8.00(1H, d, J=3.9Hz)
29	NMR($CDCl_3$): 1.54-1.56(9H+H_2O,m), 4.00(3H, s), 6.50(1H, d, J=3.6Hz), 6.57(1H, s), 6.91(1H, d, J=3.9Hz)
30	NMR: 3.96(3H, s), 6.29(1H, d, J=3.9Hz), 6.77(1H, s), 7.09(1H, d, J=3.9Hz), 7.1 (br) m/z: 247(M^+-HCl)
31	m/z: 312(M^++H)
32	m/z: 277(M^++H)

[0066]

[Table 7]



Ex.	Sy	Ra	Rb	Rd	R^6	Re	Rf	Dat
1	-	OH	Br	Cl	H	4-Cl	H	mp.: 171-172°C
2	-	OH	Br	Cl	H	H	H	mp.:145-147°C NMR:7.54-7.63(4H,m),7.68-7.73(1H,m),7.76-7.80(2H,m),7.95(1H,d,J=2.4Hz),8.03-8.07(1H,m),8.10-8.11(1H,m),8.17(1H,d,J=2.0Hz),10.85(1H,s),12.67(br)
3	-	H	Cl	Cl	H	4-Cl	H	mp.: 169-170°C
4	-	OH	H	H	H	4-Cl	H	NMR(CDCl3): 6.92(1H,td,J=8.0, 1.2Hz), 7.03(1H,dd,J=8.8, 1.2Hz), 7.43-7.51(4H,m), 7.55-7.65(3H,m), 7.79-7.87(3H,m), 8.32(1H,s), 11.68(1H,s)
5	-	OAc	H	H	H	4-Cl	H	NMR(CDCl3): 2.32(3H,s), 7.16(1H,dd,J=7.6, 0.8Hz), 7.36(1H,td,J=7.6, 1.6Hz), 7.43-7.56(4H,m), 7.58-7.64(2H,m), 7.78(1H,dd,J=8.8, 2.4Hz), 7.81-7.86(3H,m), 8.15(1H,brs)
6	-	OAc	Br	Cl	Ac	4-Cl	H	Anal calcd. for $C_{24}H_{16}BrCl_2NO_5$. 0.75H_2O : C,51.23;H,3.13;N,2.49;Br,14.20;Cl,12.60. found : C,51.08;H,2.91;N,2.49;Br,14.07;Cl,12.94
7	-	OAc	Br	Cl	H	4-Cl	H	NMR(CDCl3): 2.37(3H,s), 7.43-7.52(3H,m), 7.56-7.66(2H,m), 7.67-7.77(3H,m), 7.81-7.86(2H,m), 7.94(1H,brs)

[0067]

[Table 8]

8	-	OMe	Br	Cl	Me	4-Cl	H	NMR(CDCl3): 3.46(3H,s), 3.86(3H,s), 7.07-7.14(3H,m), 7.29(1H,m), 7.44-7.52(3H,m), 7.56-7.65(3H,m)
9	-	OH	Br	Cl	H	4-OEt	H	mp.: 188-189°C
10	-	OH	Br	Cl	H	4-OMe	H	mp.: 179-180°C
11	-	OH	Br	Cl	H	4-F	H	mp.: 139-140°C
12	-	NH_2	H	Cl	H	4-Cl	H	mp.: 167-168°C
30	1	OH	Cl	H	H	4-Cl	H	mp.: 198-199°C
31	1	OH	Cl	Cl	H	4-Cl	H	mp.: 169-170°C
32	1	OH	H	OH	H	4-Cl	H	mp.: 236-237°C(dec)
33	1	OH	H	Me	H	4-Cl	H	mp.: 195-196°C
34	1	H	Br	Br	H	4-Cl	H	mp.: 180-181°C
35	1	OH	H	Cl	H	4-Cl	H	mp.: 208-209°C NMR(CDCl3): 6.94(1H,d,J=9.2Hz), 7.33(1H,dd,J=8.8, 2.4Hz), 7.44(1H,d,J=8.8Hz), 7.50(2H,t,J=8.0Hz), 7.63(1H,t,J=7.2Hz), 7.79(1H,d,J=2.4Hz), 7.82-7.87(2H,m), 7.96(1H,dd,J=8.8, 2.4Hz), 8.10(1H,d,J=3.2Hz), 10.36(1H,s), 11.92(1H,brs)
36	1	OH	H	F	H	4-Cl	H	mp.: 195-196°C NMR: 7.00(1H,dd,J=9.3, 4.8Hz), 7.31(1H,td,J=8.4, 3.0Hz),7.56-7.80(7H,m), 7.88-7.95(2H,m), 10.59(1H,brs), 11.35(1H,brs)
37	1	OH	H	Br	H	4-Cl	H	mp.: 225-226°C
38	1	OMe	Br	Cl	H	4-Cl	H	mp.: 137-138°C NMR: 3.81(3H,s),7.56-7.64(3H,m), 7.68-7.80(4H,m), 7.85-7.89(2H,m), 7.95(1H,d,J=2.4Hz), 10.79(1H,brs)
39	1	OH	Br	Cl	H	4-Cl	Cl	mp.: 212-215°C
40	1	OH	Br	Cl	H	4-Cl	Br	mp.: 207-210°C
41	1	OH	Br	Cl	H	4-Cl	F	mp.: 157-160°C NMR:7.43(2H,t,J=8.8Hz),7.67(1H,d,J=8.6Hz),7.83-7.95(5H,m),8.13(1H,d,J=2.1Hz),10.84(1H,brs),12.48(1H,brs)

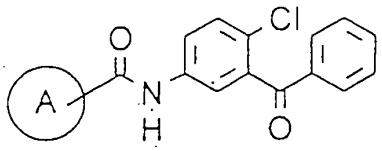
[0068]

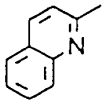
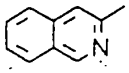
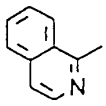
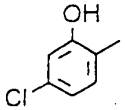
[Table 9]

42	1	OH	Br	Cl	H	4-Cl	Me	mp.: 203-206°C
43	1	OH	Br	Cl	H	4-Cl	OMe	mp.: 189-193°C
44	2	OH	Br	Cl	H	2-Cl	H	mp.: 191-194°C NMR:7.57-7.62(2H,m),7.65-7.74(2H,m),7.77-7.81(3H,m),7.97(1H,d,J=2.4Hz),8.13(1H,d,J=2.8Hz),8.21(1H,d,J=2.0Hz),11.17(1H,brs)
45	2	OH	Br	Cl	H	4-AcNH	H	mp.: 267-268°C(dec)
46	2	OH	Br	Cl	H	4-Br	H	mp.: 185-186°C NMR: 7.59(2H,t,J=7.8Hz), 7.70-7.86(6H,m), 7.93(1H,d,J=2.1Hz), 8.10(1H,d,J=2.1Hz)
47	2	OH	H	OMe	H	4-Cl	H	mp.: 178-179°C NMR: 3.74(3H,s), 6.93(1H,d,J=8.7Hz), 7.07(1H,dd,J=8.7, 3.0Hz), 7.42(1H,d,J=3.3Hz), 7.55-7.64(3H,m), 7.70-7.80(3H,m), 7.88-7.94(2H,m), 10.59(1H,s), 11.06 (1H,s)
48	2	OH	H	NO_2	H	4-Cl	H	mp.: 235-236°C
49	3	H	H	H	H	4-Cl	H	NMR(CDCl3): 7.43-7.50(5H,m), 7.54-7.63(3H,m), 7.82-7.88(5H,m), 8.06(1H,brs)
50	3	H	H	Cl	H	4-Cl	H	NMR(CDCl3): 7.41-7.48(4H,m), 7.53(1H,ddd,J=8.8, 2.0, 1.2Hz), 7.57-7.65(2H,m), 7.73(1H,dt,J=8.0, 1.2Hz), 7.82-7.87(4H,m), 8.00(1H,brs)
51	3	H	Br	H	H	4-Cl	H	NMR(CDCl3): 7.35(1H,t,J=8.0Hz), 7.43(1H,d,J=8.8Hz), 7.47(2H,t,J=8.0Hz), 7.58(1H,d,J=2.4Hz), 7.63(1H,tt,J=8.0, 1.2Hz), 7.67(1H,ddd,J=8.0, 2.0, 0.8Hz), 7.76-7.83(3H,m), 7.85(1H,dd,J=8.8, 2.4Hz), 8.01(1H,t,J=2.0Hz), 8.15(1H,brs)
52	1	OH	Br	Cl	H	4-Me	H	mp.: 163-166°C
53	1	OH	Br	Cl	Me	4-Cl	H	mp.: 160-163°C

[0069]

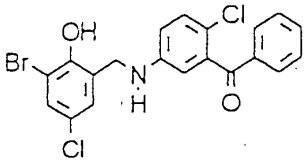
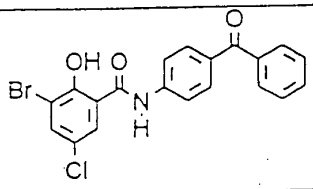
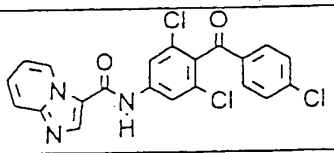
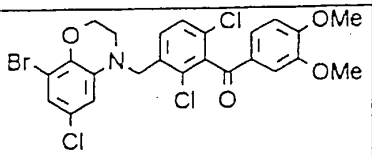
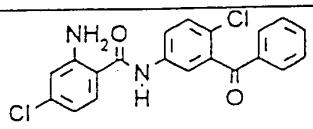
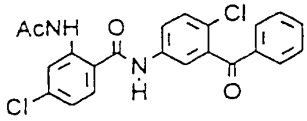
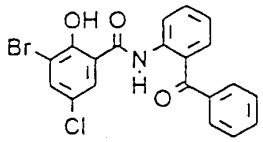
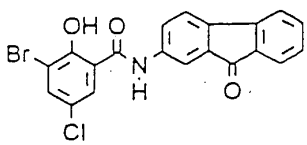
[Table 10]



Ex.	Sy	A	Dat
54	1		NMR(CDCl3): 7.39-7.49(5H,m), 7.57(1H,d,J=2.4Hz), 7.61(1H,tt,J=7.2, 1.2Hz), 7.82-7.86(4H,m), 8.00(1H,dd,J=2.0, 1.2Hz)
55	1		mp.: 173-174°C
56	1		mp.: 129-130°C
57	1		mp.: 196-197°C
58	1		mp.: 195-196°C
59	1		mp.: 128-129°C NMR: 7.47-7.52(1H,m), 7.56-7.66(4H,m), 7.70-7.80(3H,m), 8.04-8.11(2H,m), 8.27(1H,dd,J=4.4, 1.1Hz), 11.18(1H,s), 11.79(1H,s)
60	1		mp.: 191-192°C
61	1		mp.: 204-205°C
62	1		mp.: 154-155°C
63	1		mp.: 212-213°C NMR: 7.02-7.05(2H,m), 7.56-7.63(3H,m), 7.71-7.79(3H,m), 7.85-7.89(2H,m), 7.92(1H,dd,J=8.8,2.4Hz), 10.55(1H,brs), 11.80(1H,brs)

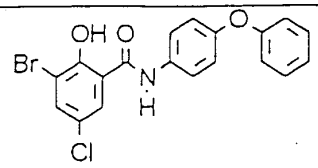
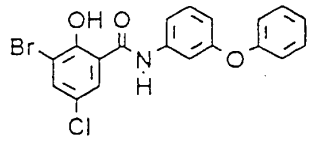
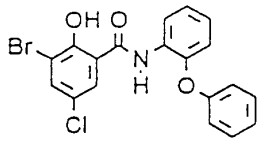
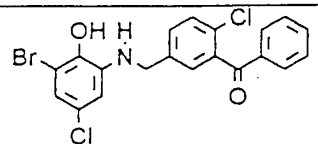
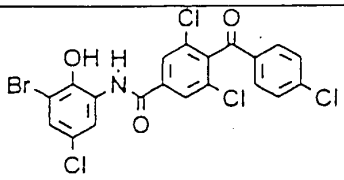
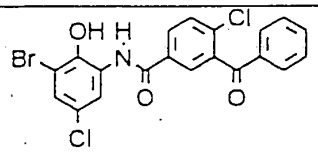
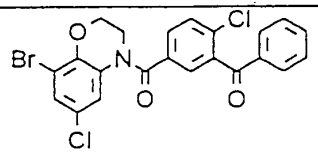
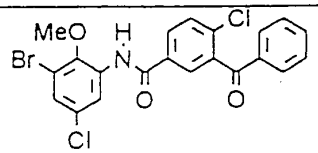
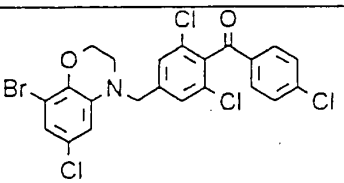
[0070]

[Table 11]

Ex.	Sy	Str	Dat
13	-		NMR(CDCl3): 4.30-4.39(3H,m), 6.63(1H,brs), 6.65(1H,d,J=2.8Hz), 6.71(1H,dd,J=8.4, 2.8Hz), 7.16(1H,d,J=2.4Hz), 7.24(1H,d,J=7.2Hz), 7.41(1H,d,J=2.4Hz), 7.46(2H,t,J=8.0Hz), 7.57-7.62(1H,m), 7.79-7.84(2H,m)
14	-		mp.: 213-216°C NMR:7.55-7.61(2H,m),7.66-7.71(1H,m),7.73-7.77(2H,m),7.82(2H,d,J=8.8Hz),7.91(2H,d,J=8.8Hz),7.95(1H,d,J=2.8Hz),8.16(1H,d,J=2.8Hz),10.97(1H,s)
15	-		mp.: 229-231°C NMR(CDCl3): 7.08-7.12(1H,m), 7.46-7.52(3H,m), 7.76-7.82(5H,m), 7.91(1H,brs), 8.28(1H,brs), 9.51-9.53(1H,m)
16	-		mp.: 205-206°C
17	-		mp.: 179-181°C
18	-		mp.: 222-225°C NMR: 2.07(3H,s), 7.30(1H,dd,J=8.3,2.4Hz), 7.57-7.64(3H,m), 7.71-7.79(4H,m), 7.87-7.92(2H,m), 8.21(1H,d,J=2.0Hz), 10.38(1H,brs), 10.72(1H,brs)
64	2		mp.: 203-206°C
65	2		mp.: >300°C NMR:7.34-7.39(1H,m),7.59-7.64(2H,m),7.77(1H,d,J=7.6Hz),7.82(1H,d,J=8.4Hz),7.88(1H,dd,J=8.0,1.6Hz),7.94(1H,d,J=2.0Hz),8.03(1H,d,J=1.6Hz),8.16(1H,d,J=2.0Hz),10.86(1H,s),12.59(1H,brs)

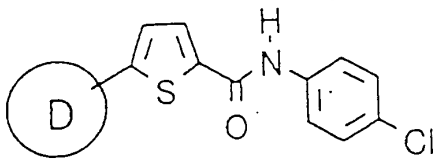
[0071]

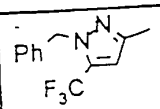
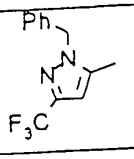
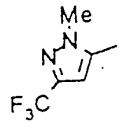
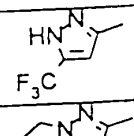
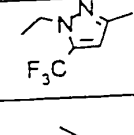
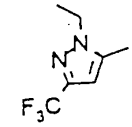
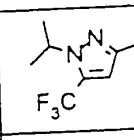
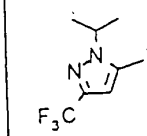
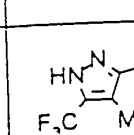
[Table 12]

66	2		NMR(CDCl3): 7.00-7.06(4H,m), 7.13(1H,tt, J=7.3, 1.1Hz), 7.32-7.39(2H,m), 7.44-7 .53(3H,m), 7.70(1H,d,J=2.6Hz), 8.02(1 H,brs), 12.36(1H,s)
67	2		NMR(CDCl3): 6.86(1H,dt,J=7.0, 2.2Hz), 7. 04-7.07(2H,m), 7.15(1H,tt,J=7.3, 1.1Hz), 7.23-7.26(1H,m), 7.30-7.40(4H,m), 7.50(1H,d,J=2.2Hz), 7.70(1H,d,J=2.6Hz), 7.96(1H,brs), 12.20(1H,s)
68	2		mp.: 144-145°C
69	13		mp.: 166-167°C
70	1		mp.: 235-237°C NMR(CDCl3): 6.30(1H,s),7.32(1H,d,J=2.4H z),7.48-7.51(2H,m),7.75-7.78(2H,m),7.8 8(2H,s),8.31(1H,d,J=2.4Hz),8.38(1H,brs)
71	1		mp.: 184-185°C
72	1		NMR: 3.90-3.93(2H,m), 4.44-4.47(2H,m), 7.29(1H,br), 7.50(1H,d,J=2.5Hz), 7.54-7.58(2H,m), 7.66-7.78(5H,m), 7.81(1H, dd,J=8.3,2.5Hz)
73	14		mp.: 156-157°C
74	16		mp.: 193-194°C NMR: 3.46(2H,m), 4.39(2H,m), 4.47(2H,s), 6.49(1H,d,J=2.0Hz), 6.93(1H,d,J=2.0H z), 7.27(2H,s), 7.47(2H,dt,J=8.4,2.0Hz) , 7.76(2H,dt,J=8.4,2.0Hz)

[0072]

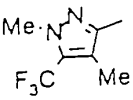
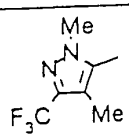
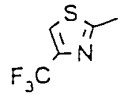
[Table 13]



Ex.	Sy	D	Dat
19	-		mp.: 190-192°C NMR(CDCl3): 5.45(2H,s), 6.89(1H,s), 7.26-7.29(2H, m), 7.31-7.35(6H,m), 7.55-7.61(4H,m)
20	-		m/z:462(FAB,M+1) NMR(CDCl3): 5.53(2H,s), 6.76(1H,s), 7.01(1H,d,J=3.9Hz), 7.05-7.08(2H,m), 7.29-7.36(5H,m), 7.51(1H,d,J=3.9Hz), 7.53-7.61(3H,m)
75	1		mp.:204-206°C NMR: 4.09(3H, s), 7.18(1H, s), 7.44(2H, d, J=8.7Hz), 7.64(1H, d, J=4.4Hz), 7.78(2H, d, J=9.3Hz), 8.10(1H, d, J=4.0Hz), 10.48(1H, s)
76	1		mp.: 246-247°C
77	1		mp.: 220-221°C
78	1		mp.: 177°C NMR(CDCl3): 1.51(3H,t,J=7.3Hz), 4.36(2H,q,J=7.3Hz), 6.69(1H,s), 7.21(1H,d,J=3.9Hz), 7.34-7.38(2H,m), 7.56-7.60(2H,m), 7.61(1H,d,J=3.9Hz), 7.66(1H,brs)
79	1		mp.: 188-190°C
80	1		mp.: 205-210°C NMR(CDCl3): 1.54(6H,d,J=6.8Hz), 4.73-4.83(1H,m), 6.64(1H,s), 7.17(1H,d,J=3.9Hz), 7.34-7.37(2H,m), 7.56-7.60(2H,m), 7.61(1H,d,J=3.4Hz), 7.67(1H,brs)
81	1		mp.: 276-278°C NMR: 2.30(3H, s), 7.44(2H, d, J=8.8Hz), 7.57(1H, d, J=3.9Hz), 7.78(2H, d, J=8.8Hz), 8.09(1H, d, J=3.9Hz), 10.46(1H, s), 14.09(1H, s)
82	25		mp.: 203-206°C

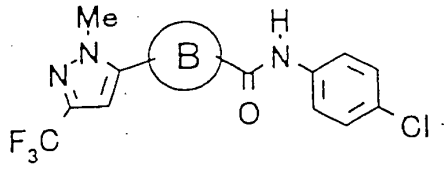
[0073]

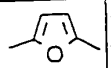
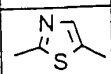
[Table 14]

83	19		mp.: 210-213°C NMR: 2.32-2.36(3H, m), 3.99(3H, s), 7.42(2H, d, J=8.8Hz), 7.49(1H, d, J=3.7Hz), 7.77(2H, d, J=9.1Hz), 8.03(1H, d, J=3.8Hz), 10.39(1H, s)
84	20		mp.: 192-196°C NMR: 2.15(3H, s), 3.91(3H, s), 7.44(2H, d, J=9.2Hz), 7.50(1H, d, J=4.3Hz), 7.77(2H, d, J=9.1Hz), 8.14(1H, d, J=3.7Hz), 10.50(1H, s)
85	1		m/z : 389(FAB,M+1) NMR: 7.44(2H,d,J=8.8Hz), 7.78(2H,d,J=8.8Hz), 7.94(1H,d,J=3.9Hz), 8.07(1H,d,J=3.9Hz), 8.59(1H,brs), 10.52(1H,brs)

[0074]

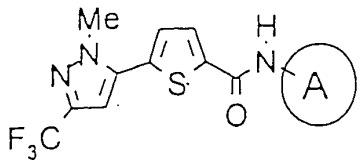
[Table 15]



Ex.	Sy	B	Dat
86	1		mp.: 183-185°C NMR(CDCl3): 4.13(3H,s), 6.78(1H,d,J=4.0Hz), 6.89(1H,s), 7.33-7.37(3H,m), 7.59-7.64(2H,m), 7.96(1H,brs)
87	3		mp.: 163-164°C NMR: 4.28(3H,s), 7.43-7.48(2H,m), 7.55(1H,s), 7.73-7.78(2H,m), 8.75(1H,s), 10.69(1H,brs)

[0075]

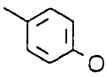
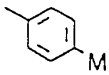
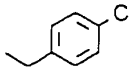
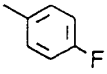
[Table 16]



Ex.	Sy	A	Dat
21	-		mp.: 156°C NMR(CDCl3): 4.08(3H, s), 6.74(1H, s), 7.13(1H, td, J=7.8, 1.5Hz), 7.24-7.27(1H, m), 7.32-7.37(1H, m), 7.44(1H, dd, J=7.8, 1.5Hz), 7.66(1H, d, J=3.9Hz), 8.32(1H, s), 8.48(1H, dd, J=8.3, 1.4Hz)
22	-		mp.: 158-159°C NMR: 3.44(3H, s), 4.07(3H, s), 5.90-5.92(1H,m), 5.98(1H, t, J=3.2Hz), 6.67-6.70(1H, m), 7.16(1H, s), 7.62(1H, d, J=3.9Hz), 8.03(1H, d, J=3.9Hz), 10.12(1H, s)
23	-		mp. :247°C(dec) Anal calcd. for $C_{15}H_{11}F_3N_4OS$. HCl: C, 46.34; H, 3.11; N, 14.41; S, 8.25; Cl, 9.12; F, 14.66. found: C, 46.19; H, 2.99; N, 14.39; S, 8.13; Cl, 9.07; F, 14.72.

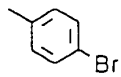
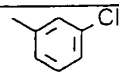
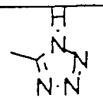
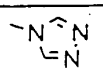
[0076]

[Table 17]

- 24	-	Et	mp.: 136-137°C NMR: 1.14(3H, t, J=7.1Hz), 3.25-3.31(2H, m), 4.05(3H, s), 7.11(1H, s), 7.54(1H, d, J=3.9Hz), 7.81(1H, d, J=3.9Hz), 8.65(1H, t, J=5.4Hz)
88	1		mp.: 185-186°C NMR: 4.08(3H, s), 6.76(2H, d, J=8.8Hz), 7.15(1H, s), 7.48(2H, d, J=8.8Hz), 7.61(1H, d, J=3.9Hz), 8.04(1H, d, J=3.9Hz), 9.32(1H, s), 10.17(1H, s)
89	3		mp.: 167-169°C NMR(CDCl3): 2.35(3H, s), 4.06(3H, s), 6.72(1H, s), 7.19(2H, d, J=8.3Hz), 7.22(1H, d, J=3.9Hz), 7.49(2H, d, J=8.3Hz), 7.60(1H, d, J=3.9Hz), 7.65(1H, s)
90	3		mp.: 159-161°C NMR(CDCl3): 2.35(3H, s), 4.06(3H, s), 6.72(1H, s), 7.13-7.18(1H, m), 7.22(1H, d, J=3.9Hz), 7.23-7.30(2H, m), 7.58(1H, s), 7.61(1H, d, J=3.9Hz), 7.86(1H, d, J=7.8Hz)
91	3		mp.: 181-183°C NMR(CDCl3): 4.08(3H, s), 6.74(1H, s), 7.25-7.27(1H, m), 7.32(1H, dd, J=9.1, 2.2Hz), 7.45(1H, d, J=2.4Hz), 7.66(1H, d, J=3.9Hz), 8.25(1H, s), 8.45(1H, d, J=8.8Hz)
92	3		mp.: 147-148°C NMR: 4.08(3H, s), 7.18(1H, s), 7.22-7.36(3H, m), 7.59(1H, t, J=7.8Hz), 7.64(1H, d, J=3.9Hz), 8.10(1H, d, J=3.9Hz), 10.33(1H, s)
93	21		mp.: 129-130°C NMR(CDCl3): 4.07(3H, s), 6.72(1H, s), 7.16-7.21(1H, m), 7.23(1H, d, J=3.4Hz), 7.37-7.42(2H, m), 7.60-7.63(3H, m), 7.66(1H, s)
94	21		mp.: 126-127°C NMR(CDCl3): 4.04(3H, s), 4.61(2H, d, J=5.9Hz), 6.30-6.40(1H, m), 6.68(1H, s), 7.17(1H, d, J=3.4Hz), 7.27-7.35(4H, m), 7.49(1H, d, J=3.9Hz)
95	25		mp.: 189-192°C NMR: 4.09(3H, s), 7.17-7.25(3H, m), 7.64(1H, d, J=3.9Hz), 7.72-7.77(2H, m), 8.09(1H, d, J=3.9Hz), 10.42(1H, brs)

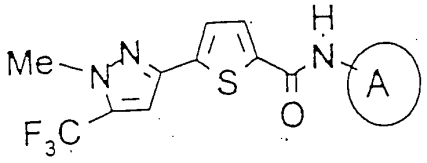
[0077]

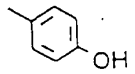
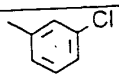
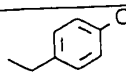
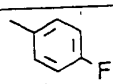
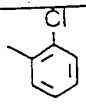
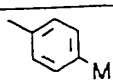
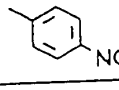
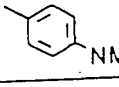
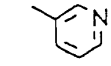
[Table 18]

96	25		mp.: 191-192°C NMR($CDCl_3$): 4.07(3H, s), 6.73(1H, s), 7.24(2H, d, J=3.9Hz), 7.49-7.54(3H, m), 7.62(1H, d, J=3.9Hz), 7.67(1H, brs)
97	25		mp. :127-129°C
98	3		mp.: 285-287°C(dec)
99	3		mp.: 180-185°C Anal calcd. for $C_{14}H_{10}F_3N_3OS_2$. $0.25H_2O$: C, 46.47; H, 2.92; N, 11.61; S, 17.72; F, 15.75. found: C, 46.37; H, 2.71; N, 11.44; S, 17.72; F, 15.65.
100	3		mp.: 186-187°C NMR($CDCl_3$): 4.07(3H, s), 6.73(1H, s), 7.25(1H, d, J=3.9Hz), 7.35(1H, dd, J=8.3, 4.8Hz), 7.68(1H, d, J=3.9Hz), 7.95(1H, s), 8.26(1H, ddd, J=8.3, 3.0, 1.4Hz), 8.42(1H, dd, J=4.7, 1.7Hz), 8.68(1H, d, J=2.5Hz)
101	3		mp.: 166-168°C NMR($CDCl_3$): 4.07(3H, s), 6.72(1H, s), 7.13(1H, dd, J=4.9, 1.5Hz), 7.23(1H, d, J=3.9Hz), 7.31(1H, dd, J=5.2, 3.2Hz), 7.60(1H, d, J=3.9Hz), 7.68(1H, d d, J=3.0, 1.5Hz), 7.97(1H, s)
102	21		mp.: 235-238°C NMR: 4.09(3H, s), 7.20(1H, s), 7.28-7.31(1H,m), 7.57(1H, d, J=3.9Hz), 7.65(1H, d, J=3.9Hz), 8.28(1H, brs), 12.94(1H, brs)
103	21		mp.:207-210°C
104	25		mp.: 140-141°C NMR: 1.10-1.20(1H, m), 1.24-1.37(4H, m), 1.58-1.66(1H, m), 1.69-1.79(2H, m), 1.79-1.89(2H, m), 3.67-3.78(1H, m), 4.05(3H, s), 7.10(1H, s), 7.53(1H, d, J=3.9Hz), 7.87(1H, d, J=3.9Hz), 8.38(1H, d, J=7.8Hz)

[0078]

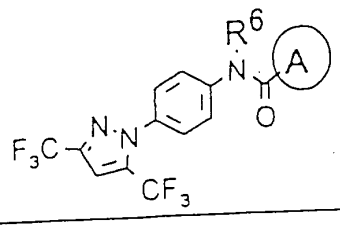
[Table 19]

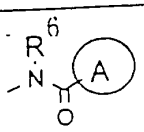
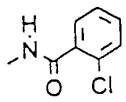
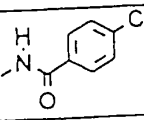
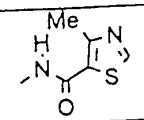
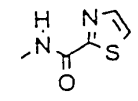
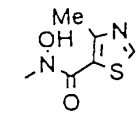
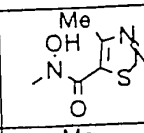
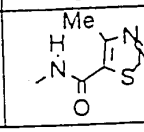


Ex.	Sy	A	Dat
25	-		mp.: 244-246°C
105	1		mp.: 223-224°C
106	1		mp.: 156-157°C
107	1		mp.: 182-183°C
108	1		mp.: 197-199°C
109	3		mp.: 224-226°C
110	21		mp.: 155-157°C
111	21		mp.: 205-207°C
112	21		mp.: 234-236°C
113	25		mp.: 230°C
114	1		mp.: 195-196°C
115	25		mp.: 211-215°C
116	25		mp.: 207°C(dec)
138	21		mp.: 241-242°C

[0079]

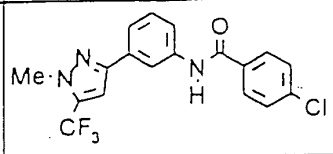
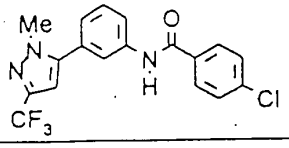
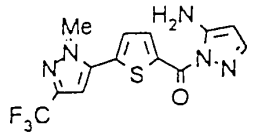
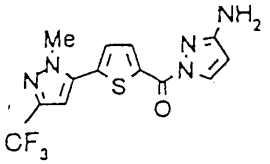
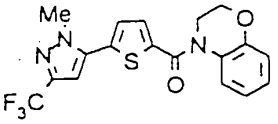
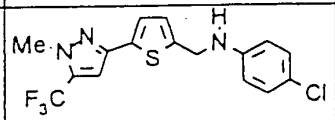
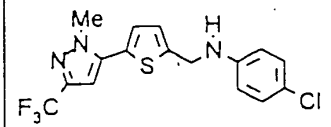
[Table 20]



Ex.	Sy		Dat
117	1		mp.: 183-185°C NMR: 7.49(1H, td, J=7.3, 1.0Hz), 7.54(1H, td, J=7.6, 1.9Hz), 7.59-7.67(4H, m), 7.82(1H, s), 7.93(2H, d, J=9.3Hz), 10.88(1H, s)
118	3		mp.: 196-197°C NMR: 7.60-7.67(4H, m), 7.82(1H, s), 7.99-8.04(4H, m), 10.64(1H, s)
119	1		mp.: 144-145°C NMR: 2.64(3H, s), 7.61(2H, d, J=8.8Hz), 7.82(1H, s), 7.90(2H, d, J=8.8Hz), 9.17(1H, s), 10.57(1H, s)
120	1		mp.: 174-175°C NMR: 7.63(2H, d, J=8.8Hz), 7.83(1H, s), 8.10(2H, d, J=8.8Hz), 8.15(1H, d, J=2.9Hz), 8.19(1H, d, J=3.4Hz), 11.17(1H, s)
121	25		m/z: 437(FAB, M+1) NMR(CDCl3): 2.60(3H, s), 7.09(1H, s), 7.51(2H, d, J=9.2Hz), 7.75(2H, d, J=8.8Hz), 8.87(1H, s), 9.72(1H, brs)
122	1		mp.: 126-129°C NMR(CDCl3): 2.94(3H, s), 7.10(1H, s), 7.53(2H, d, J=8.8Hz), 7.92(2H, d, J=8.3Hz), 10.15(1H, brs)
123	1		mp.:166-168°C NMR: 2.84(3H, s), 7.65(2H, d, J=8.8Hz), 7.83(1H, s), 7.91(2H, d, J=9.2Hz), 11.05(1H, s)

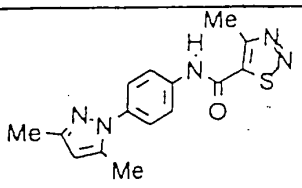
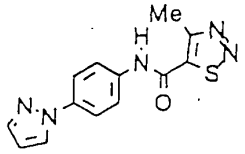
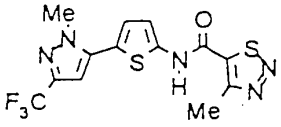
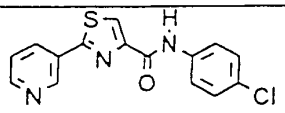
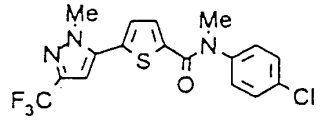
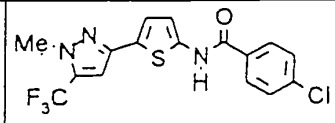
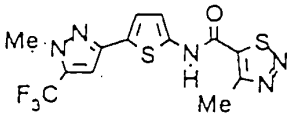
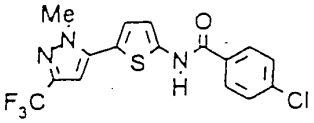
[0080]

[Table 21]

Ex.	Sy	Str	Dat
26	-		mp.: 173-175°C
27	-		mp.:150-153°C
28	-		mp. : 126-128°C NMR: 4.09(3H,s), 5.44(1H,d,J=2.0Hz), 6.86(2H,brs), 7.22(1H,s), 7.58(1H,d,J=2.0Hz), 7.66(1H,d,J=4.4Hz), 8.30(1H,d,J=4.4Hz)
29	-		mp. : 144-146°C NMR: 4.10(3H,s), 5.89(2H,brs), 6.07(1H,d,J=3.4Hz), 7.17(1H,s), 7.65(1H,d,J=3.9Hz), 8.22(1H,d,J=3.4Hz), 8.31(1H,d,J=3.9Hz),
124	3		mp.: 153-155°C
125	13		mp.: 113-115°C
126	13		mp.: 92-94°C NMR(CDCl3): 3.99(3H, s), 4.18(1H, brs), 4.53(2H, d, J=4.9Hz), 6.58-6.63(3H, m), 7.01-7.04(1H, m), 7.06(1H, d, J=3.9Hz), 7.14(2H, d, J=8.8Hz)

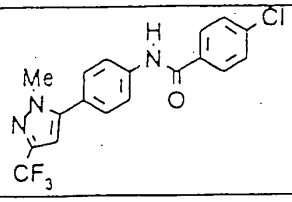
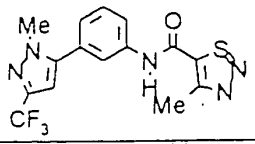
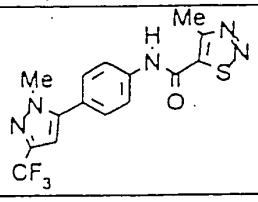
[0081]

[Table 22]

Ex.	Sy	Str	Dat
127	1		mp.: 101-103°C
128	1		mp.: 184-186°C
129	1		mp.: 148-149°C NMR: 2.86(3H,s), 4.03(3H, s), 6.97-6.98 (2H,m), 7.35(1H,d,J=4.0Hz), 12.32(1 H,brs)
130	21		mp.:135-138°C
131	25		mp.:136-137°C NMR: 3.35(3H, s), 3.96(3H, s), 6.55(1H, d, J=3.9Hz), 7.03(1H, s), 7.31(1H, d, J=3.9Hz), 7.46(2H, d, J=8.7Hz), 7.55(2H, d, J=8.3Hz)
132	25		mp.: 197-199°C
133	25		mp.: 140°C Anal calcd. for $C_{13}H_{10}F_3N_5OS_2$. $0.25H_2O$: C, 41.32; H, 2.80; N, 18.53; S, 1 6.97; F, 15.08. found: C, 41.59; H, 2.59; N, 18.52; S, 16.68; F, 15.24.
134	25		mp.: 166-168°C NMR: 4.03(3H, s), 6.93(1H, s), 7.01(1H, d, J=4.4Hz), 7.33(1H, d, J=3.9Hz), 7.67(2H, d, J=8.3Hz), 8.05(2H, d, J=8.8Hz), 11.92(1H, s)

[0082]

[Table 23]

Ex.	Sy	Str	Dat
135	26		mp.:187-188°C NMR(CDCl3): 3.93(3H,s), 6.56(1H,s), 7.42-7.45(2H,m), 7.48-7.51(2H,m), 7.75-7.79(2H,m), 7.82-7.86(2H,m), 7.91(1H,brs)
136	26		NMR:2.83(3H, s), 3.95(3H, s), 6.92(1H, s), 7.41(1H, d, J=7.3Hz), 7.56(1H, t, J=7.8Hz), 7.78(1H, d, J=7.8Hz), 7.90-7.92(1H, m), 10.91(1H, brs)
137	26		m/z:368(FAB, M^++1) NMR:2.82(3H, s), 3.94(3H, s), 6.91(1H, s), 7.61-7.65(2H, m), 7.82-7.86(2H, m), 10.93(1H, brs)

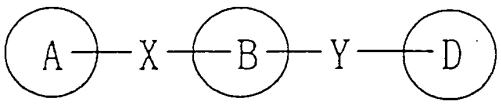
[Name of Document] Abstract

[Abstract]

[Problem] The provision of a Ca^{2+} release-activated Ca^{2+} channel inhibitor (CRACC) useful for prevention or treatment of various inflammatory diseases

[Means for Solving the Problem] - Novel amide or amine derivative represented by the following general formula (I) or a pharmaceutically acceptable salt thereof as well as a medicament comprising the same as an active ingredient.

[Chemical formula 1]



(I)

(symbols in the formula having the following meanings:

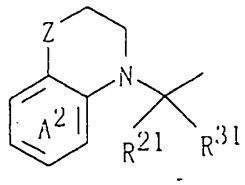
A represents an aryl group which may be substituted; an aralkyl which may be substituted; a heteroaryl which may be substituted and which may be condensed, cycloalkyl or lower alkyl

X represents a group represented by the formula $-NR^1-CR^2R^3-$ or the formula $-CR^4R^5-NR^6-$ (R^1 and R^6 represent H, OH, lower alkyl, lower alkyl-O- or lower alkyl-CO- group,

R^2 and R^3, R^4 and R^5 may be the same or different, and represent both H or together form an oxo (=O) group),

or A and X together form a group represented by the formula

[Chemical formula 2]



wherein A^2 represents a benzene ring which may be substituted, R^{21} and R^{31} represent similar groups to R^2 and R^3 ; Z represents O or NR^7; R^7 represents H or a lower alkyl group,

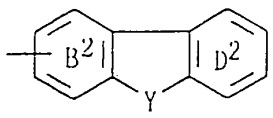
B represents an arylene group which may be substituted or a monocyclic heteroarylene group which may be substituted,

Y represents a single bond, O, S, CO, CS, SO_2 or SO,

D represents an aryl group which may be substituted or a heteroaryl group which may be substituted and which may be condensed,

or B, Y and D together form a group represented by the formula

[Chemical formula 3]



wherein Y has the same definition as described above; B^2 and D^2 represent a benzene ring which may be substituted.)

[Selected Drawing] Nil